Diagnosis and Management of Carbohydrate-Induced Diarrhea

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Learning Objectives

Upon completion of this activity, participants should be better able to:

- Explain the pathophysiology of carbohydrate-induced diarrhea
- Utilize current diagnostic approaches
- Provide individualized and appropriate management to meet specific patient needs
- Educate patients and parents on etiology and physiologic consequences as well as the importance of dietary modifications

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Target Audience

- This activity is designed for pediatricians, pediatric and adult gastroenterologists, primary care physicians, physician assistants, nurse practitioners, dietitians, and other health care professionals who are interested in treating children and young adults with carbohydrate-induced diarrhea.

AMA PRA Statement

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Disclosures

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Faculty Disclosures

Looi Ee, MBBS has nothing to disclose.

Martín G. Martín, MD has nothing to disclose.

John F. Pohl, MD has nothing to disclose.

Yul Reinstein, MD has nothing to disclose.

J. Marc Rhoads, MD has nothing to disclose.

Robert Shulman, MD has nothing to disclose.

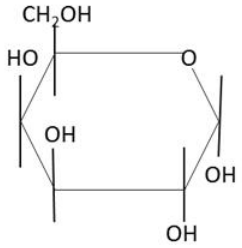
Emily Contreras, MD has nothing to disclose.

Martin H. Ulshen, MD has nothing to disclose.

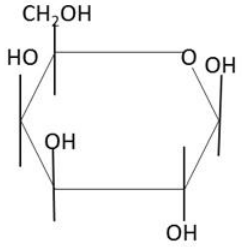
General Principles

Common Dietary Carbohydrates: Monosaccharides

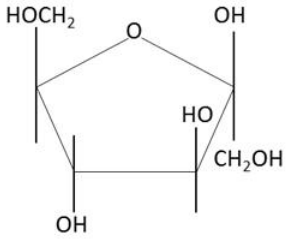
Glucose



Galactose

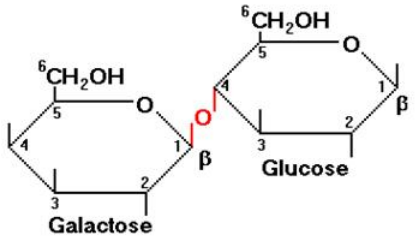


Fructose

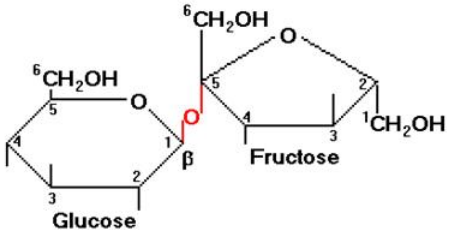


Common Dietary Carbohydrates: Disaccharides and Starches

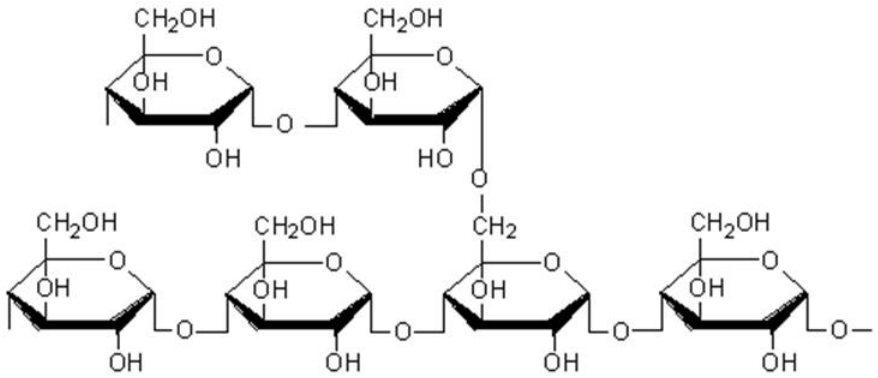
Lactose



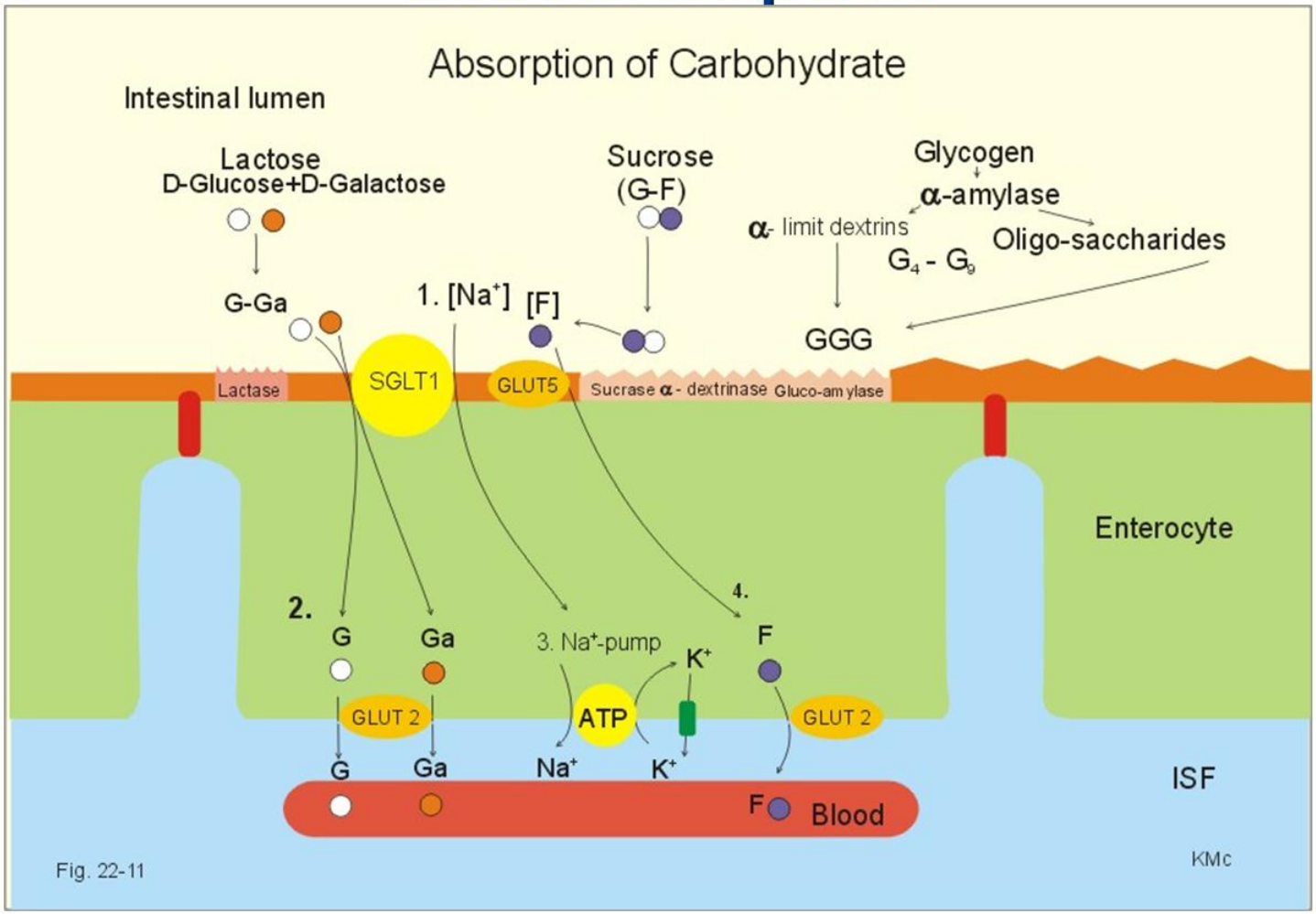
Sucrose



Starches



Overview of Carbohydrate Digestion and Absorption



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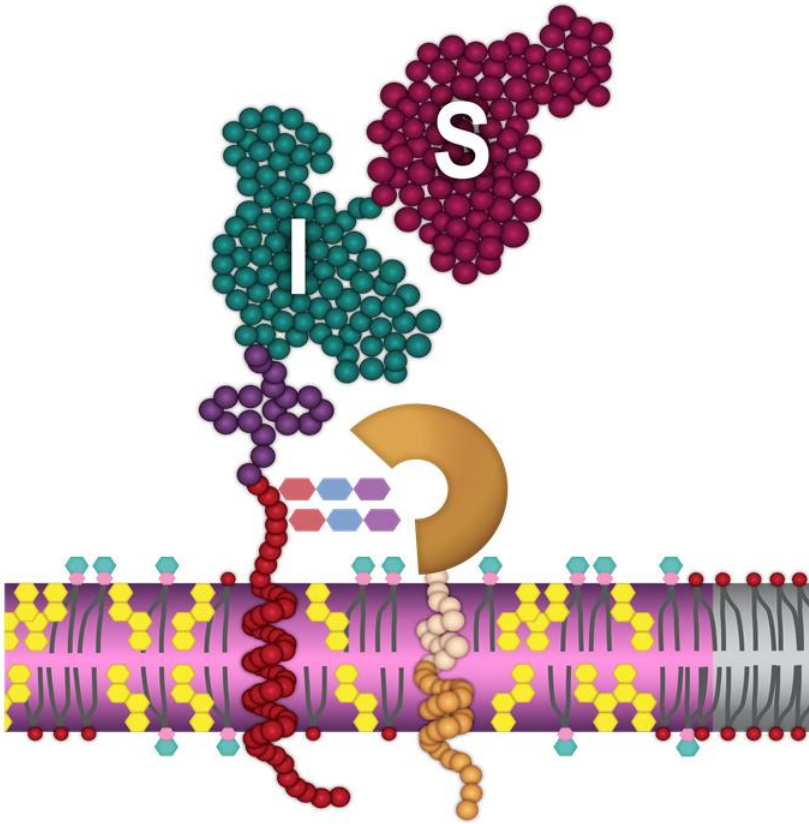
Paulev P-E and Zubieta-Calleja G. *New Human Physiology*. 2nd ed. http://www.zuniv.net/physiology/book/chapter22.html. Accessed February 15, 2013.

Disaccharidases

- Membrane-bound glycoproteins located within microvilli
- Luminal I active site
- Two main classes:
  - α-glycosidases
    - Sucrase-isomaltase, maltase-glucoamylase, trehalase
  - β-glycosidases
    - Lactase



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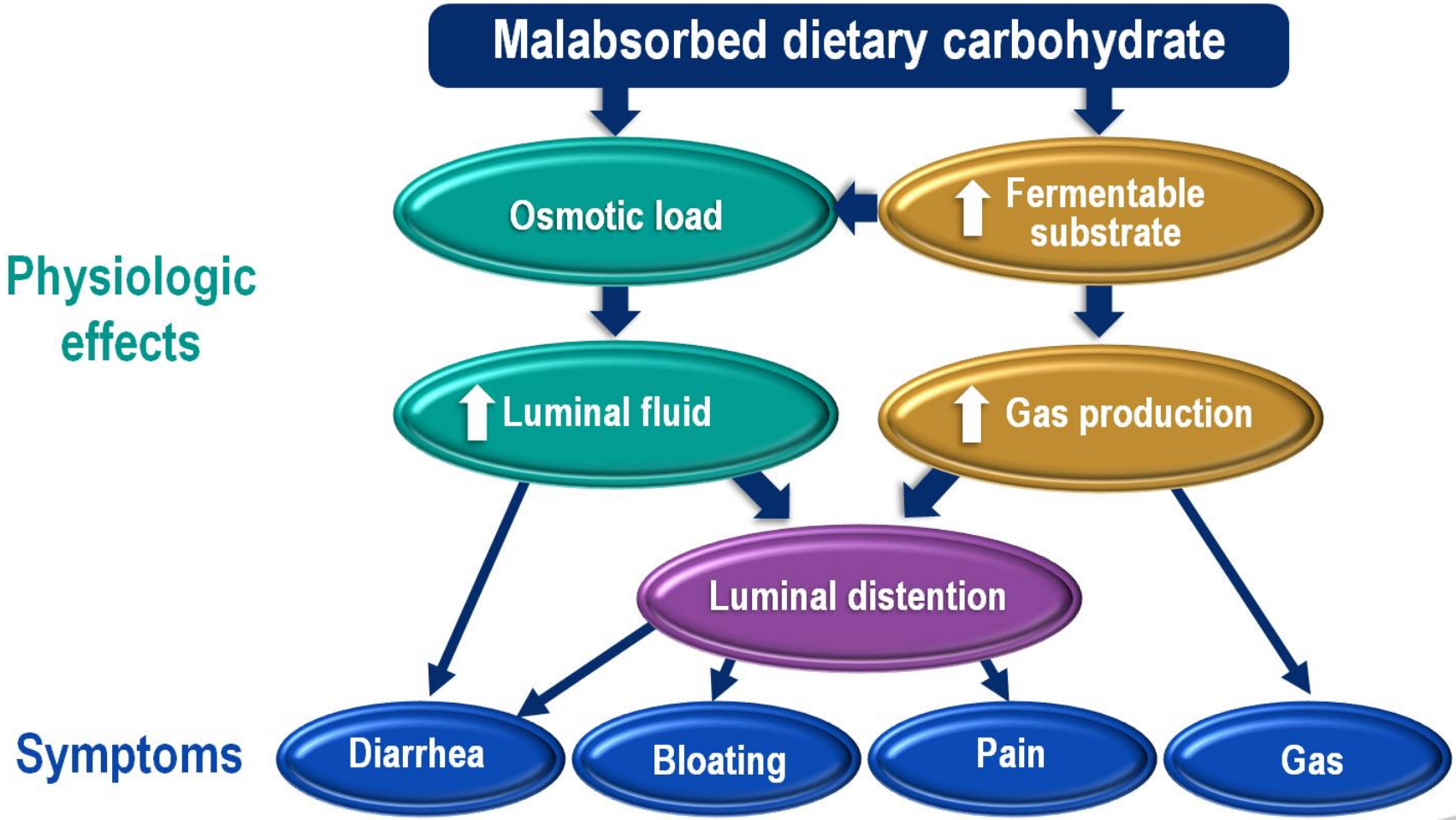
Tori AJ, et al. *J Pediatr Gastroenterol Nutr*. 2007;45:194-198.
Gupta SK, et al. *J Pediatr Gastroenterol Nutr*. 1999;28:246-251.
Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.

Fermentation of Malabsorbed Carbohydrate

- Incompletely digested carbohydrates pass into the colon
- Anaerobic bacteria ferment malabsorbed carbohydrate to:
  - Hydrogen and methane gas
    - Excreted in breath (basis of breath hydrogen testing)
  - Short-chain fatty acids
    - Absorbed, providing energy to colonic epithelial cells and systemically
    - Are osmotically active, contributing to diarrhea

Macfarlane GT and Macfarlane S. *J Clin Gastroenterol*. 2011;45(Suppl):S120-S127.

Carbohydrate Malabsorption: Pathogenesis of Symptoms



Barrett JS and Gibson PR. *Pract Gastroenterol*. 2007;31:51-65.

Carbohydrate Malabsorption: Diagnosis

- Signs and symptoms
  - Diarrhea
  - Abdominal pain
  - Bloating and flatulence
  - Failure to thrive in infants - rare
- History
  - Age at presentation
  - Careful nutritional history

Tori AJ, et al. *J Pediatr Gastroenterol Nutr*. 2007;45:194-198.
Gupta SK, et al. *J Pediatr Gastroenterol Nutr*. 1999;28:246-251.
Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.

Carbohydrate Maldigestion/Malabsorption Disorders: Typical Age of Onset

1-7 days

Glucose-galactose malabsorption
Congenital lactase deficiency
Sucrase-isomaltase deficiency

3-6 months

Fructose malabsorption
Glucoamylase deficiency
Sucrase-isomaltase deficiency

3-15 years

Fructose malabsorption
Adult-onset lactase deficiency

Martín MG and Wright EM. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management, 5th ed.* Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.
Tori AJ, et al. *J Pediatr Gastroenterol Nutr*. 2007;45:194-198.
Gupta SK, et al. *J Pediatr Gastroenterol Nutr*. 1999;28:246-251.
Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.

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Carbohydrate Malabsorption Disorders: Diagnosis

- Stool testing (nonspecific)
  - pH < 6
  - Positive for reducing substances
    - Glucose, galactose, fructose
    - Not sucrose – but may be detectable from bacterial degradation to glucose and fructose
  - Increased osmotic gap > 100 mOsm/L
    - 290 – 2 ([Na+] + [K+])
    - 290 is stool osmolality (not often measured directly)

Treem WR. ***J Pediatr Gastroenterol Nutr.*** **1995;21:1-14.**

Carbohydrate Malabsorption: Diagnosis

- Rule out inflammatory process[1]
  - Occult blood
  - Calprotectin
    - Value is age-dependent[2-4]

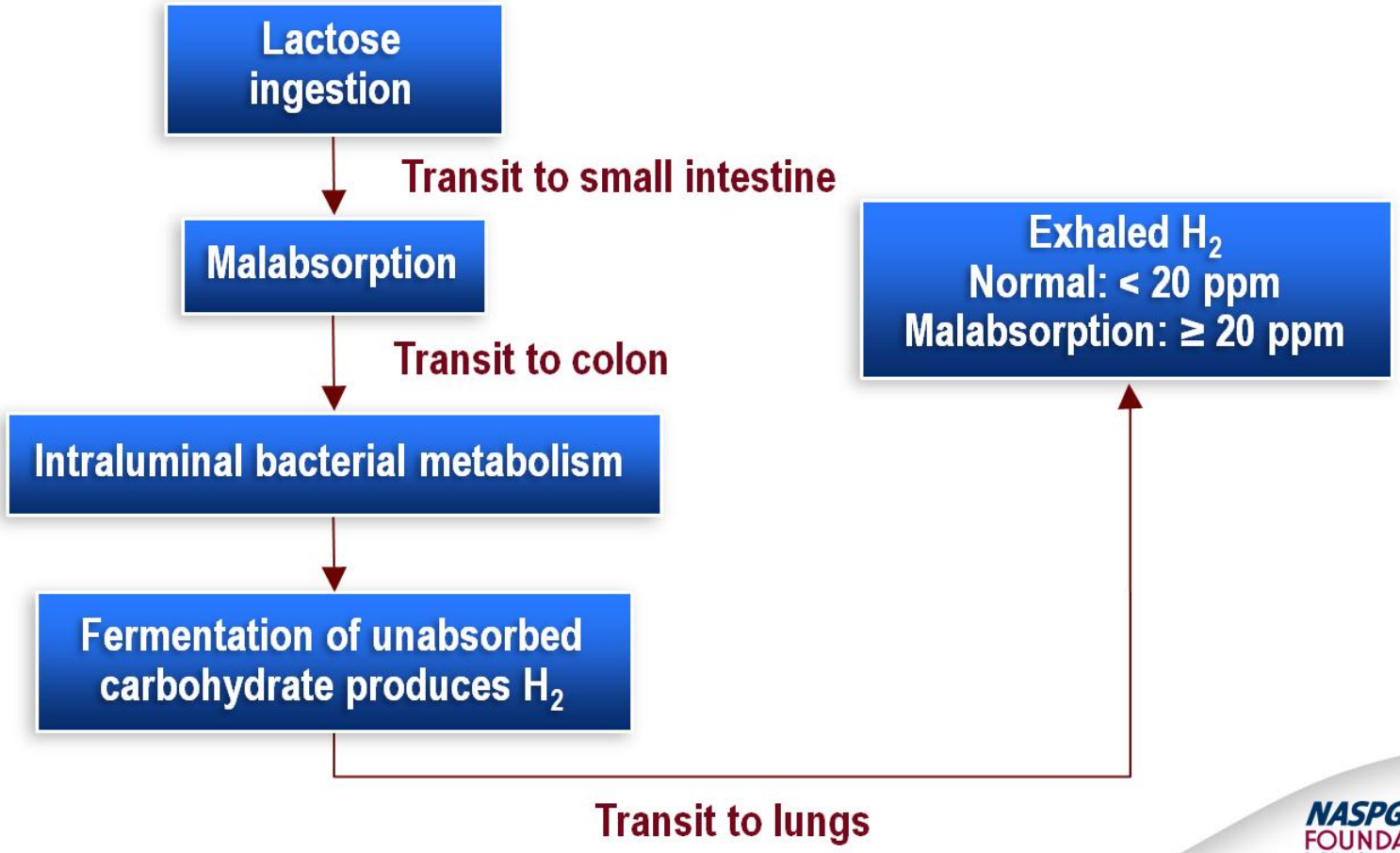
[1]Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.
[2]Kapel N, et al. *J Pediatr Gastroenterol Nutr*. 2010;51:542-547.
[3]Baldassarre ME, et al. *Immunopharmacol Immunotoxicol*. 2011;33:220-223.
[4]Carroccio A, et al. *Clin Chem*. 2003;49:861-867.

Carbohydrate Malabsorption: Diagnosis

- Breath hydrogen tests
  - Predicated on fermentation of malabsorbed carbohydrate by colonic bacteria
  - Malabsorption defined as a specific rise in parts per million (ppm) of H_2 over the baseline value

Carbohydrate Malabsorption: Diagnosis

Production of H_2 Following Lactose Ingestion



Carbohydrate Malabsorption: Diagnosis

- Dietary exclusion
  - Often nonspecific because of difficulty in excluding potential offending carbohydrate
  - Often subjective response in the case of developmental lactase deficiency

Suarez FL, et al. *N Engl J Med*. 1995;333:1-4.
Suarez FL, et al. *Am J Clin Nutr*. 1997;65:1502-1506.

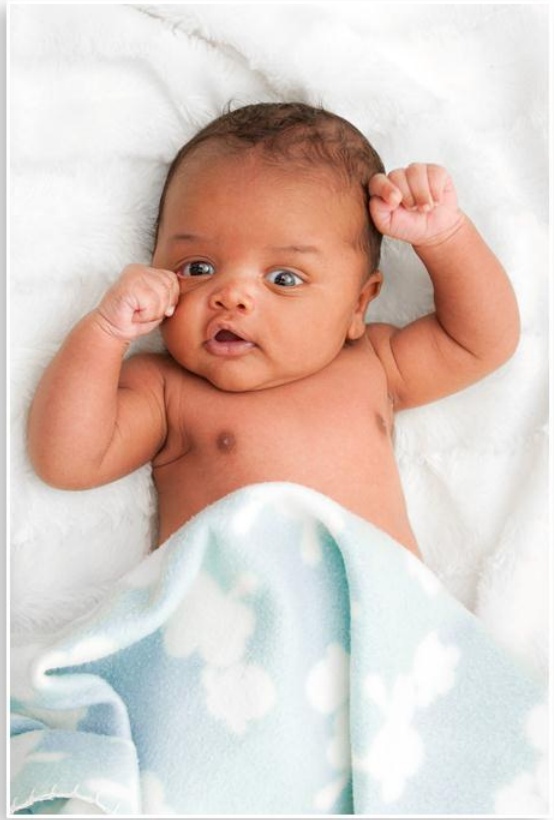
Carbohydrate Malabsorption: Diagnosis

- Duodenal or jejunal biopsy - histology and disaccharidase activity (document site of biopsy)
  - Enzyme activities most commonly assayed are sucrase, lactase, and maltase
  - Isomaltase is measured using palatinase substrate
  - Gold standard for diagnosis of congenital sucrase-isomaltase deficiency (CSID)
  - Requires proper handling and processing of biopsy samples

Glucose-Galactose Malabsorption

Case Study: Alice

- 1-week-old African American female
- Infant is discharged on the day after delivery and parents immediately note watery diarrhea

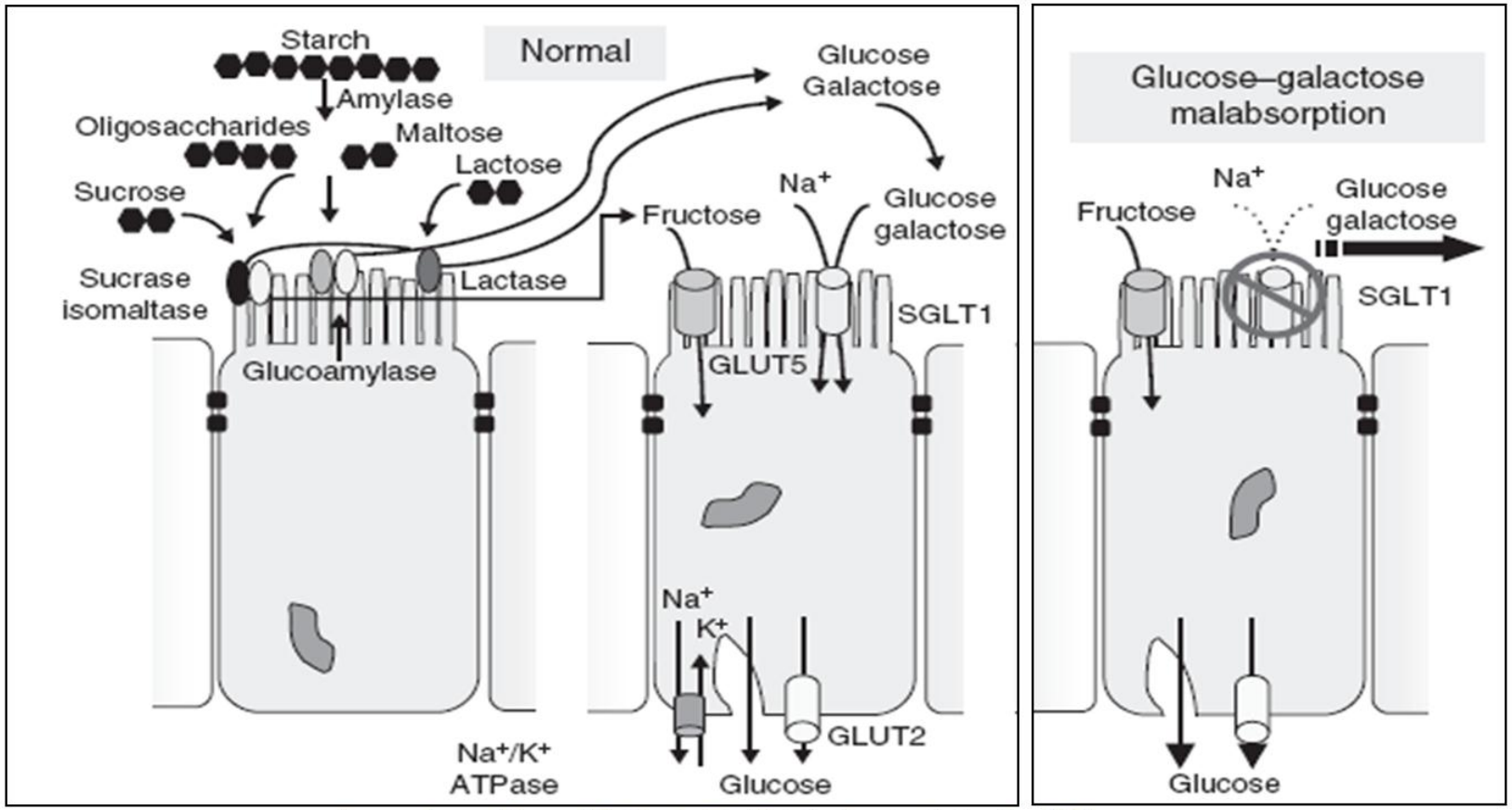


Glucose-Galactose Malabsorption

- Distinguishing feature[1]
  - Onset of diarrhea - first week of life
  - Selective malabsorption of glucose/galactose
- Inheritance[1]
  - Autosomal recessive
    - Parents without symptoms
    - Associated with consanguinity
- Molecular basis[2,3]
  - Defect sodium/glucose cotransporter protein
  - Mutation of SGLT1 gene (SLC5a1)

[1]Genetics Home Reference Web site. http://ghr.nlm.nih.gov/condition/glucose-galactose-malabsorption. Published October 30, 2012. Accessed February 15, 2013.
[2]Turk E, et al. *Nature*. 1991;350:354-356.
[3]Martin MG, et al. *Nat Genet*. 1996; 12:216-220.

Glucose-Galactose Malabsorption Pathophysiology



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Martín MG and Wright EM. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management,* 5th ed. Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.

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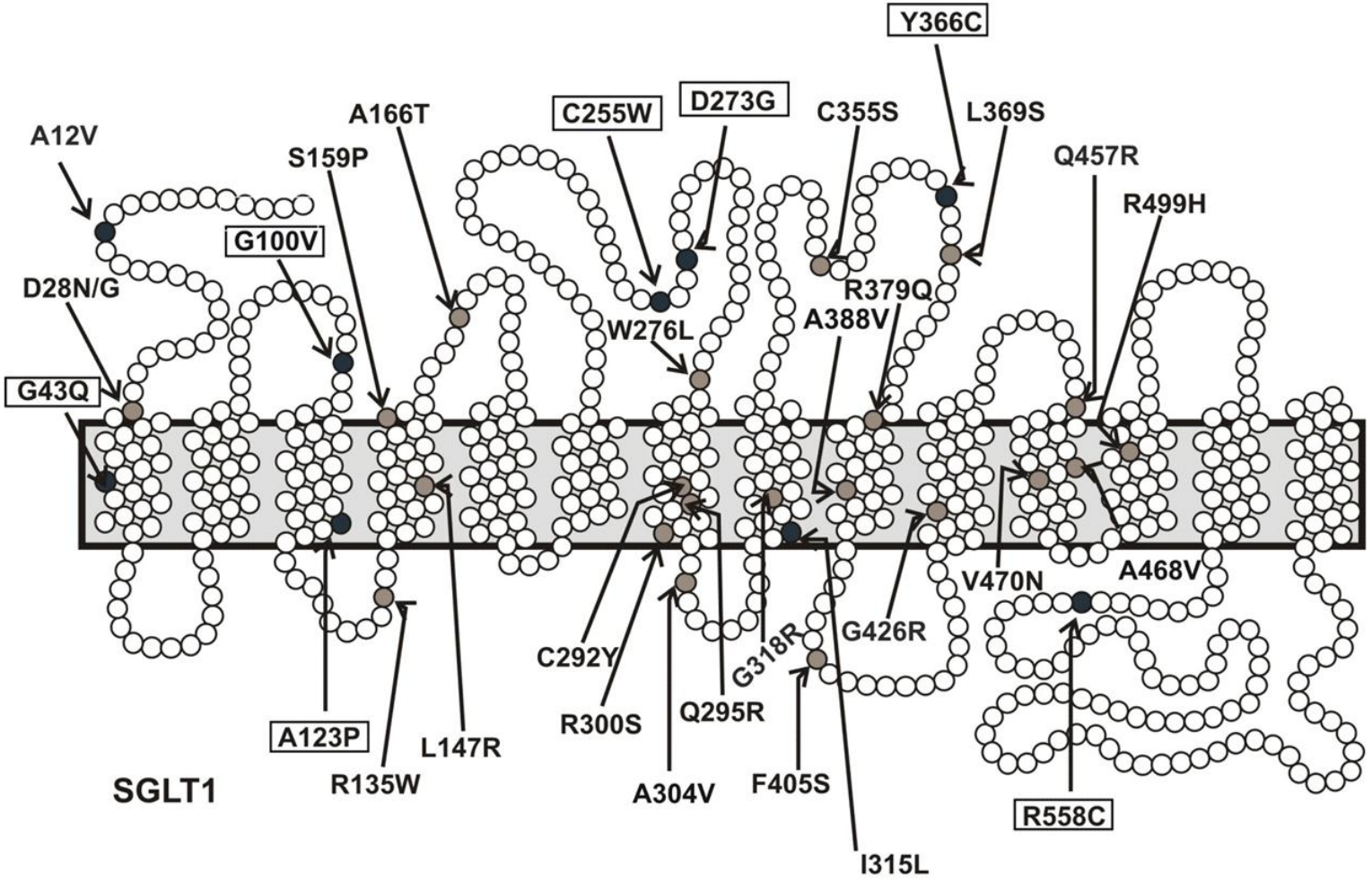
Glucose-Galactose Malabsorption: SGLT1 - Missense Mutations



Martín MG and Wright EM. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management*, 5th ed. Volume 1. Hamilton, Ontario, Canada: BC Decker Inc.; 2008.

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Glucose-Galactose Malabsorption: Diagnosis

- Present with osmotic diarrhea during first week of life
  - Severe metabolic acidosis
  - Stool pH < 6, positive for reducing substances with increased osmotic gap
- Sibling with similar history
- Occasional glucosuria
- Small bowel biopsies - normal
- Selective malabsorption of glucose and galactose

Martín MG and Wright EM. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management,* 5th ed. Volume 1. Hamilton, Ontario, Canada: BC Decker Inc.; 2008.

Glucose-Galactose Malabsorption: Diagnosis

- Meticulous recording of intake and output
- Dietary challenge - tolerance/intolerance not subtle
  - Glucose-containing rehydration solution - diarrhea
  - Carbohydrate-free formula (RCF®) - no diarrhea
  - Carbohydrate-free formula with 6%-8% fructose - no diarrhea
  - Carbohydrate-free formula with 1% glucose - diarrhea
- Glucose breath testing - malabsorption (optional)
- SGLT1 gene sequencing - many mutations (optional)

Martín MG and Wright EM. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management,* 5th ed. Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.

Glucose-Galactose Malabsorption: Treatment

- Lifetime restriction of glucose and galactose (modified Atkins diet)
- Galactose - monosaccharide primarily in lactose
- Some reports of marginal improvement in glucose tolerance with age
- First 12 months of life, carbohydrate-free formula (RCF®) with addition of fructose required

Martín MG and Wright EM. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management,* 5th ed. Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.

Glucose-Galactose Malabsorption: Treatment

- When solids are introduced
  - Pureed food
  - Glucose-free
  - Protein/fat and fructose-based
- Many patients stay on carbohydrate-free formula with fructose beyond 12 months, but not required
- Adequate dietary calcium via supplementation must be provided

Martín MG and Wright EM. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management,* 5th ed. Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.

Glucose-Galactose Malabsorption: Education

- Early input of dietitian
  - May require multiple visits centering around education
- Parents need to become familiar with the amount of glucose/galactose in a broad group of foods
- Managing diet early in life relatively easy, but more difficult later
  - With independence and exploration, controlling glucose intake more difficult

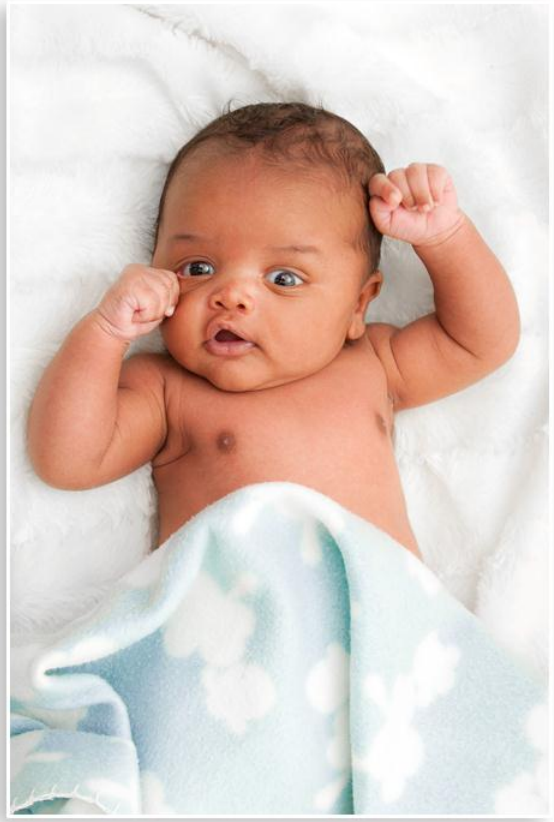
Martin MG and Wright EM. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management*, 5th ed. Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.

Glucose-Galactose Malabsorption: Education

- Parents should be encouraged to explore level of glucose tolerance
- Make family aware that most liquid medicines are dissolved in glucose-based syrup; use crushed tablets instead
- High fat/protein and fructose-based diet not associated with obesity or other medical problems

Alice: Follow-Up

- Stool pH is 4.5
- Diarrhea induced with dietary challenge of glucose-containing formulas
- Alice is diagnosed with glucose-galactose malabsorption
- Carbohydrate-free formula with fructose for first 12 months
- Extensive education regarding carbohydrates in food and medications



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Fructose Malabsorption

Case Study: Manny

- 12-year-old male
- Symptoms
  - Bloating, pain, and excessive flatulence after eating
  - Symptoms manifest or worsen after eating/drinking:
    - Fruits and fruit juices
    - Soft drinks
    - Pizza

Dietary Fructose

- Dietary fructose
  - 64%-95% from sucrose and high-fructose corn syrup (HFCS)
  - Remainder from free fructose and fructans (linear or branched fructose polymers; perhaps 10% of total intake)
  - Pizza, pasta, cakes, and breads are sources of fructans
- Intake in United States
  - Mean 49 g/day
  - Approximately 2/3 from drinks and 1/3 from fruit

Latulippe ME and Skoog SM. ***Crit Rev Food Sci Nutr.*** **2011;51:583-592.**
Gibson PR, et al. ***Aliment Pharmacol Ther.*** **2007;25:349-363.**

Fructose Malabsorption

- Isolated malabsorption is a rare disorder
  - Not due to mutations in protein coding region of GLUT5
  - Etiology unknown – may not be malabsorption, but possibly abnormal handling of fructose reaching the colon
- Absorption capacity increases with age

Wasserman D, et al. *J Clin Invest*. 1996;98:2398-2402.
Jones HF, et al. *Am J Physiol Gastrointest Liver Physiol*. 2011;300:G202-G206.

Fructose Malabsorption

- Malabsorption is directly related to dose
  - Limited ability to transport fructose
  - Malabsorption most commonly seen with excessive juice intake, with diarrheal symptoms associated with the daily consumption of > 15 mL/kg
  - GLUT5 expression is inducible by fructose, therefore slow, incremental increases in fructose may improve absorption

Wasserman D, et al. *J Clin Invest*. 1996;98:2398-2402.
Jones HF, et al. *Am J Physiol Gastrointest Liver Physiol*. 2011;300:G202-G206.

Fructose Malabsorption Versus Intolerance

Fructose Malabsorption[1]

- Dose-dependent
- Diarrhea

Hereditary Fructose Intolerance[2]

- Deficiency of fructose-1,6-bisphosphate aldolase
- Liver failure
- Vomiting
- Failure to thrive
- Does not cause diarrhea

[1]Shepherd SJ and Gibson PR. *J Am Diet Assoc*. 2006;106:1631-1639.
[2]Genetics Home Reference Website. http://ghr.nlm.nih.gov/condition/hereditary-fructose-intolerance. Published September 12, 2011. Accessed February 15, 2013.

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Fructose Malabsorption: Clinical Presentation

- Presentation related to amount of fructose ingested and individual's sensitivity to the symptoms of malabsorption
- May be differences among individuals in the ability to absorb and/or ferment fructose in the colon
- Bloating, abdominal pain, and flatulence are characteristic
- Ingestion of fructose alone more likely to induce symptoms than when ingested with glucose

Jones HF, et al. *Am J Physiol Gastrointest Liver Physiol*. 2011;300:G202-G206.
Latulippe ME and Skoog SM. *Crit Rev Food Sci Nutr*. 2011;51:583-592.
Kyaw MH and Mayberry JF. *J Clin Gastroenterol*. 2011;45:16-21.

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Fructose Malabsorption: Diagnosis by Breath Testing

- No consensus on appropriate dose for children
- Suggested dose 0.5 g/kg (maximum dose 15 g)
  - Positive test > 20 ppm over baseline
  - 30-min sampling interval for 3 hr
- Positive breath test along with subsequent symptoms may be most reliable
- Response to fructose alone may not reflect what happens when fructose is ingested with a meal

Latulippe ME and Skoog SM. *Crit Rev Food Sci Nutr*. 2011;51:583-592.
Gibson PR, et al. *Aliment Pharmacol Ther*. 2007;25:349-363.
Kyaw MH and Mayberry JF. *J Clin Gastroenterol*. 2010;45:16-21.

Fructose Malabsorption: Treatment

- Eliminate foods in which fructose is sole or main carbohydrate (fruits and honey)
  - Consumption of other foods likely to reduce symptoms
- Not all HFCSs may cause symptoms
  - HFCS-42 (42% fructose, 58% glucose) likely not to cause symptoms, as glucose in excess of fructose facilitates fructose absorption

Latulippe ME and Skoog SM. *Crit Rev Food Sci Nutr*. 2011;51:583-592.
Kyaw MH and Mayberry JF. *J Clin Gastroenterol*. 2010;45:16-21.
Jones HF, et al. *Am J Physiol Gastrointest Liver Physiol*. 2011;300:G202-G206.

Dietary Fermentable Substrates

- FODMAPs
  - **F**ermentable, **O**ligosaccharides (fructans/galactans), **D**isaccharides, **M**onosaccharides, **A**nd **P**olyols
- Ubiquitous
- Poorly absorbed, osmotically active, rapidly fermented
- Elimination from diet relieves symptoms in some adults with irritable bowel syndrome (IBS)
  - Likely related to increased gut sensitivity in IBS rather than greater malabsorption in IBS versus healthy individuals

Gibson PR, et al. *Aliment Pharmacol Ther*. 2007;25:349-363.

Dietary Fermentable Substrates

- FODMAPS are hard to avoid
  - Fructo-oligosaccharides (fructans): wheat, rye, onions, garlic, artichokes
  - Galacto-oligosaccharides: legumes
  - Lactose
  - Fructose: honey, apples, pears, watermelon, mango
  - Sorbitol: apples, pears, sugar-free mints/gums, stone fruits - peaches, nectarines, plums, apricots, cherries
  - Mannitol: mushrooms, cauliflower, sugar-free mints/gums

Barrett JS and Gibson PR. *Ther Adv Gastroenterol*. 2012;5:261-268.
Biesiekierski JR, et al. *J Hum Nutr Diet*. 2011;24:154-176.

Manny: Follow-Up

- Breath testing with 15 g of fructose resulted in 30 ppm rise of breath hydrogen over baseline
- Breath testing also induced bloating and pain
- Manny is diagnosed with fructose malabsorption
- Exclusion diet implemented to avoid foods that induce symptoms

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Lactase Deficiency

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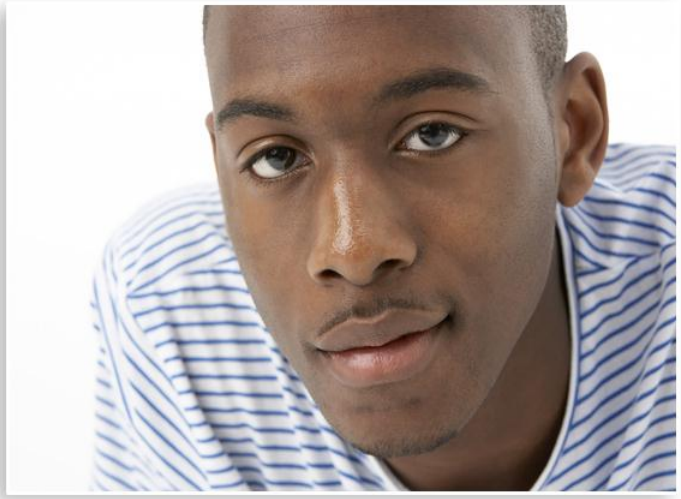
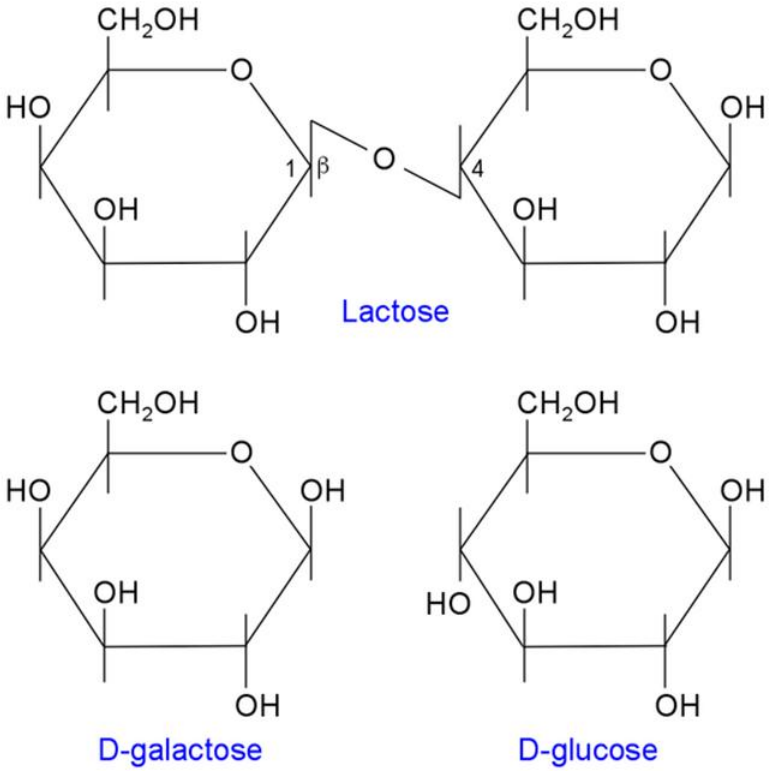
Case Study: Miles

- 15-year-old male
- Symptoms
  - Occasional diarrhea
  - Abdominal pain and bloating within 1-2 hours of eating
  - No weight loss or other constitutional symptoms



Lactose



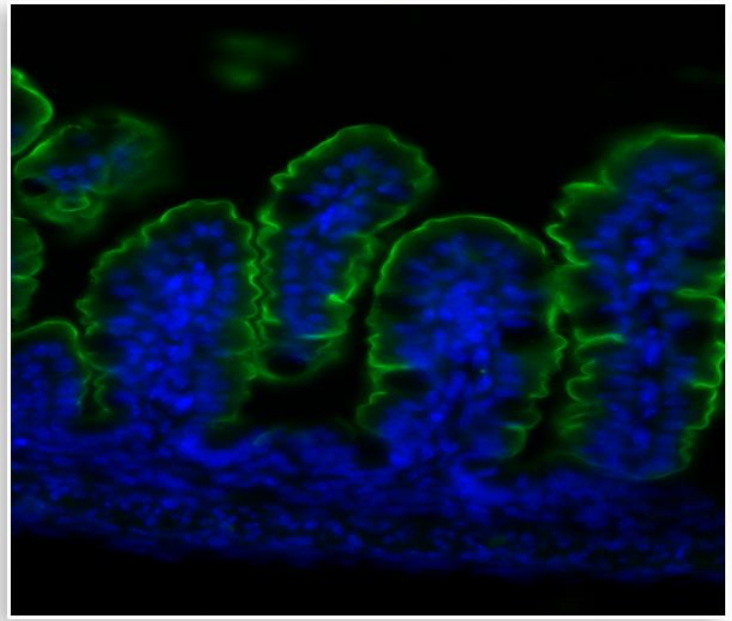
Lactose is present in milk and other dairy products

[1]Genetics Home Reference Web site. http://ghr.nlm.nih.gov/condition/lactose-intolerance. Published October 23, 2012. Accessed February 15, 2013.

Lactose Digestion

Lactose is hydrolyzed into glucose and galactose by lactase-phlorizin hydrolase, located on the tips of villi

Immunostaining of Intestinal Lactase-Phlorizin Hydrolase Protein



Genetics Home Reference Web site. http://ghr.nlm.nih.gov/gene/LCT. Published October 23, 2012. Accessed February 15, 2013.
Naim HY and Zimmer K-P. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management, 5th ed.* Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.

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Lactase Deficiency

- Primary[1]
  - Congenital lactase deficiency
  - Developmental
  - Hypolactasia - ethnic variation in severity and prevalence
- Secondary[2]
  - Mucosal injury; e.g., from celiac disease, infection, allergy, Crohn's disease
  - Bacterial overgrowth

[1]Genetics Home Reference Web site. http://ghr.nlm.nih.gov/condition/lactose-intolerance. Published October 23, 2012. Accessed February 15, 2013.
[2]Bayless TM and Diehl A. *Advanced Therapy in Gastroenterology and Liver Disease*. 5th ed. Hamilton, Ontario, Canada: BC Decker Inc; 2005.

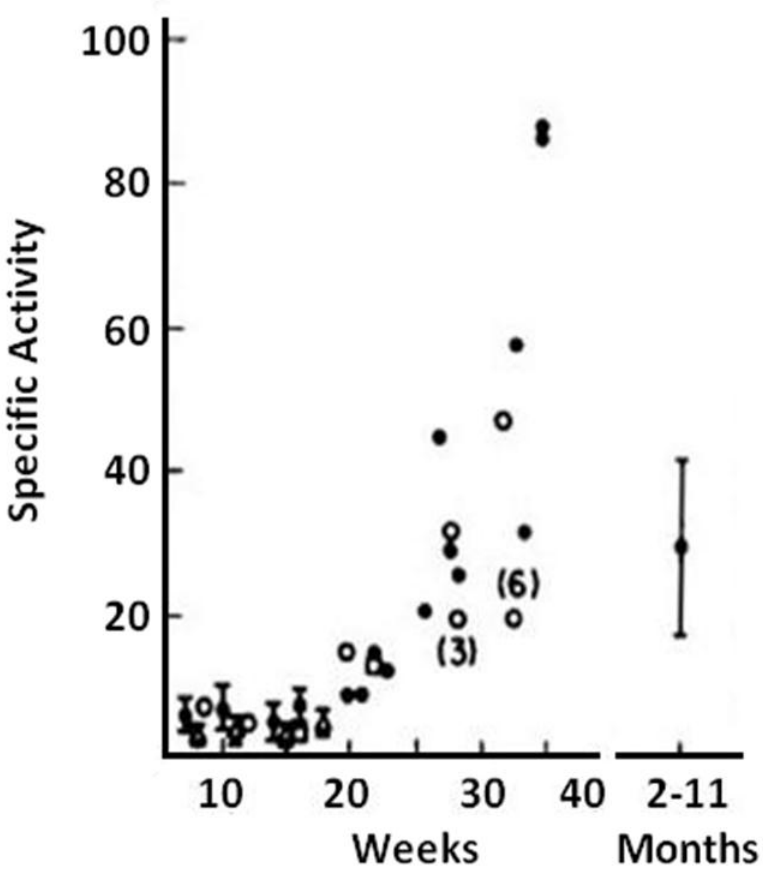
Lactase Deficiency: Congenital Lactase Deficiency

- Rare autosomal recessive disorder
- Most reported cases from Finland
- Diarrhea from birth when fed lactose-containing milk (e.g., breastmilk, cow or goat milk formula)
- Absent lactase activity, but histology and other disaccharidase levels normal

Järvelä I, et al. *Am J Hum Genet*. 1998;63:1078-1085.
Kuokkanen M, et al. *Am J Hum Genet*. 2006;78:339-344.

Lactase Deficiency: Developmental Changes in Lactase Activity

- Lactase activity increases primarily in last trimester
- Infants born < 32 weeks gestation have reduced lactase activity
- Lactase activity decreases after weaning in all mammals
- Only some humans have persistence of lactase activity after weaning



Mobassaleh M, et al. *Pediatrics.* 1985;75(Pt 2):160-166.

Lactase Deficiency: Lactase Persistence

- Lactase persistence is defined by the ability to digest lactose as an adult
- Most of the world's adult population develop hypolactasia
- Single nucleotide polymorphisms, including C/T-13910 and G/A-22018, in the coding and regulatory parts of the lactase gene have been associated with lactase expression[1]
- The T allele of 13910 is strongly associated with lactase persistence in European, but not sub-Saharan African populations[2,3]

[1]Troelsen JT. *Biochim Biophys Acta*. 2005;1723:19-32.
[2]Enattah NS, et al. *Nat Genet*. 2002;30:233-237.
[3]Mulcare CA, et al. *Am J Hum Genet*. 2004;74:1102-1110.

Lactase Deficiency: Ethnic Variation in Lactase Activity

TABLE 2
Prevalence of Primary Lactase Deficiency in Various Ethnic Groups

Group	*Prevalence (%)*
Northern Europeans	2 to 15
American whites	6 to 22
Central Europeans	9 to 23
Indians (Indian subcontinent)	
Northern	20 to 30
Southern	60 to 70
Hispanics	50 to 80
Ashkenazi Jews	60 to 80
Blacks	60 to 80
American Indians	80 to 100
Asians	95 to 100

Adapted with permission from Sahi T. Genetics and epidemiology of adult-type hypolactasia. Scand J Gastroenterol 1994;29(Suppl 202):7-20.

Swagerty DL, et al. *Am Fam Physician*. 2002;65:1845-1851.

Lactase Deficiency: Lactose Intolerance Versus Malabsorption

- Terms are often used interchangeably but are not strictly equivalent
- Individuals may malabsorb some degree of lactose but may not have symptoms of intolerance
- Alternatively, people who identify themselves as severely lactose intolerant may mistakenly attribute a variety of abdominal symptoms to lactose intolerance
- In adults, lactose intake limited to 240 mL of milk a day causes negligible symptoms

Suarez FL, et al. *N Engl J Med*. 1995;333:1-4.
Suarez FL, et al. *Am J Clin Nutr*. 1997;65:1502-1506.

Lactase Deficiency: Lactose Intolerance Versus Malabsorption

- Lactose malabsorption detected by breath H_2 test is more common than actual symptoms of lactose intolerance
- Lactose intolerance frequency varies less among different ethnic/racial groups than does lactose malabsorption
- Frequency of lactose malabsorption is low in children < 6 years of age
  - Frequency of lactose malabsorption peaks between 10 and 16 years of age

Suchy FJ, et al. *Ann Intern Med*. 2010;152:792-796.

Lactose Malabsorption With Intolerance: Clinical Presentation

- Symptoms: bloating, abdominal pain, flatulence, diarrhea, and vomiting (especially in adolescents)[1]
- Stools may be watery, frothy, and acidic[1]
- There is significant interindividual variability in symptoms
  - Symptoms are usually minimal if intake of milk < 240 mL/day[2]
  - Not all patients who report these symptoms with lactose ingestion have lactose malabsorption on breath hydrogen testing[3]

[1] Guandalini S. *Pediatric lactose intolerance*. http://emedicine.medscape.com/article/930971-overview. Modified May 11, 2012. Accessed February 15, 2013.
[2] Suarez FL, et al. *N Engl J Med*. 1995;333:1-4.
[3] Suarez FL, et al. *Am J Clin Nutr*. 1997;65:1502-1506.

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Lactose Malabsorption: Diagnostic Testing

- Stool testing[1,3]
  - pH < 6 and positive for reducing substances confirm carbohydrate malabsorption
- Lactose breath hydrogen testing[2,3]
  - 1 g/kg lactose (max 25 g) oral load after 6-hour fast
  - ≥ 20 ppm over baseline is positive
  - False positive if rapid intestinal transit
  - False negative if taking antibiotics
- Duodenal biopsy and disaccharidase analysis[3]

[1]Naim HY and Zimmer K-P. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management, 5th ed.* Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.
[2] Gasbarrini A, et al. *Aliment Pharmacol Ther*. 2009;29(Suppl 1):1-49.
[3] Montgomery RK, et al. *J Pediatr Gastroenterol Nutr*. 2007;45(Suppl 2):S131-S137.

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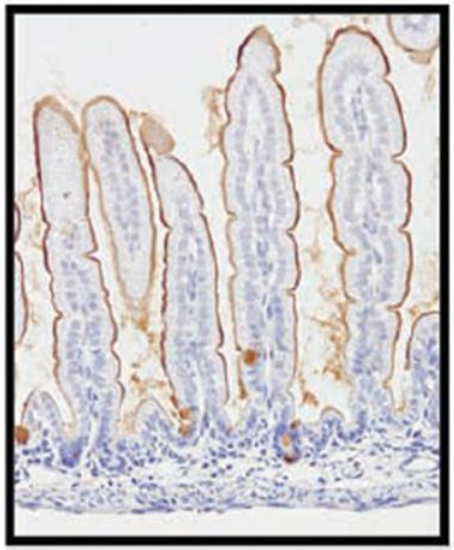
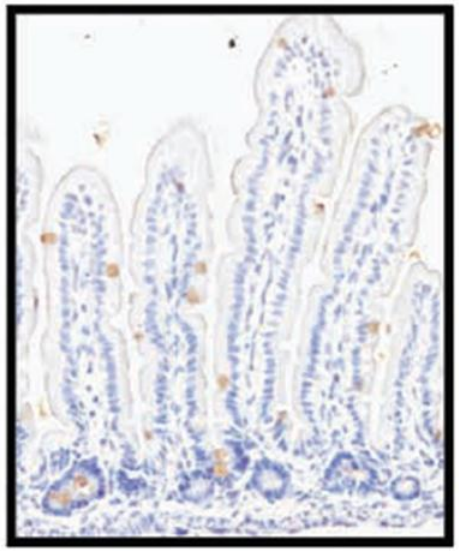
Lactase Deficiency: Diagnosis of Congenital Lactase Deficiency

- Duodenal biopsy and disaccharide analysis
  - Gold standard
  - Absent lactase activity
  - Normal histology



Immunostain for Lactase-Phlorizin Hydrolase Protein in Normal Individual



Congenital Lactase Deficiency With Absence of Protein

Image reproduced from Muncan V, et al. *Nat Commun*. 2011;2:452.

Muncan V, et al. *Nat Commun*. 201;2:452.

Lactose Malabsorption With Intolerance: Treatment

- Reduce dietary lactose intake[1]
- Enzyme replacement[2]
  - Commercially available lactase preparations are ß-galactosidases derived from yeast or bacteria
  - They are either ingested prior to eating lactose-containing foods or added to lactose-containing foods to hydrolyze lactose prior to ingestion
  - Lactose hydrolysis is often incomplete with these preparations, and symptom relief can be variable

[1]Jarvis JK and Miller GD. *J Natl Med Assoc*. 2002;94:55-66.
[2]Rosado JL, et al. *Gastroenterology*. 1984;87:1072-1082.

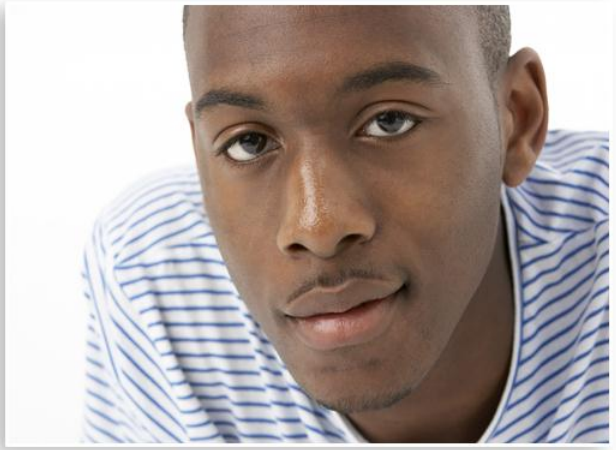
Lactose Malabsorption With Intolerance: Treatment

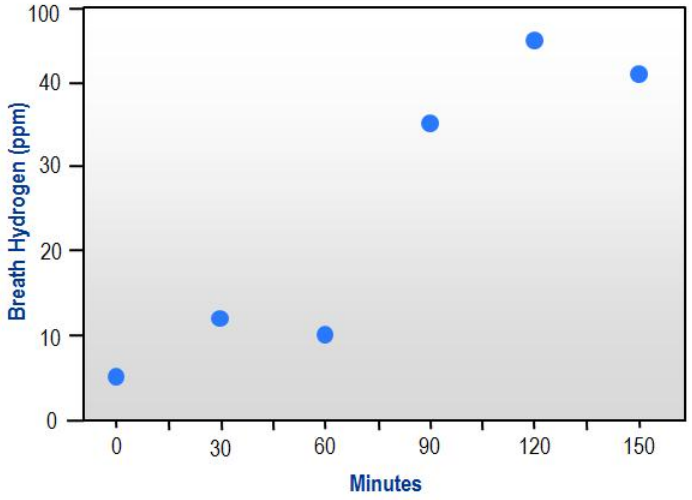
- Maintain adequate calcium intake
- Recommended daily intake
  - Infants < 1 years 260 mg
  - Age 1-3 years 700 mg
  - Age 4-8 years 1000 mg
  - Age 9-18 years 1300 mg

Institute of Medicine of the National Academies Web site. http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/DRI-Values.aspx. Published November 30, 2010. Accessed February 15, 2013.

Miles: Follow-Up

- Miles was diagnosed with hypolactasia
- Over-the-counter lactase supplement recommended when dietary lactose intake leads to intolerance
- Educated on importance of calcium supplementation if milk avoidance is required





Congenital Sucrase-Isomaltase Deficiency

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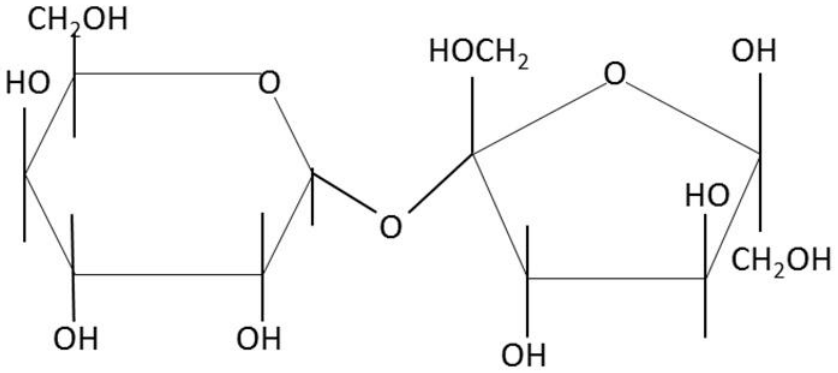
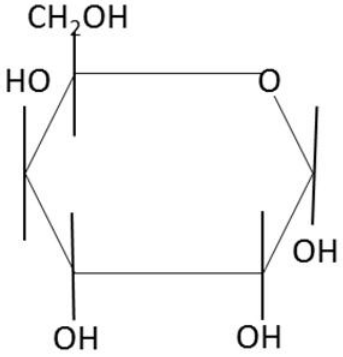
Case Study: Sarah

- 8-month-old Caucasian female
- History
  - Breastfed
  - 2-3 months of diarrhea and colicky discomfort
  - Faltered weight gain over same period
  - No vomiting and normal appetite
  - Abdominal distention after feeding

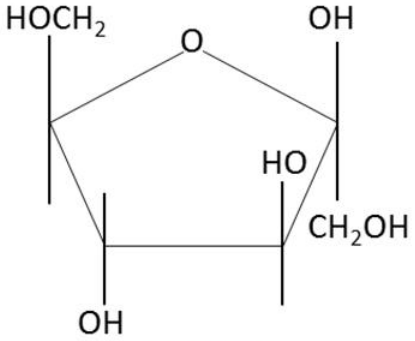
Sucrose



Sucrose



Glucose



Fructose

- Sucrose is present in fruits and table sugar

[1]Genetics Home Reference Web site. http://ghr.nlm.nih.gov/condition/congenital-sucrase-isomaltase-deficiency. Published December 2, 2012. Accessed February 15, 2013.

Sucrose Digestion

- Sucrose is hydrolyzed to glucose and fructose by sucrase-isomaltase, which is located along the length of villi[1]

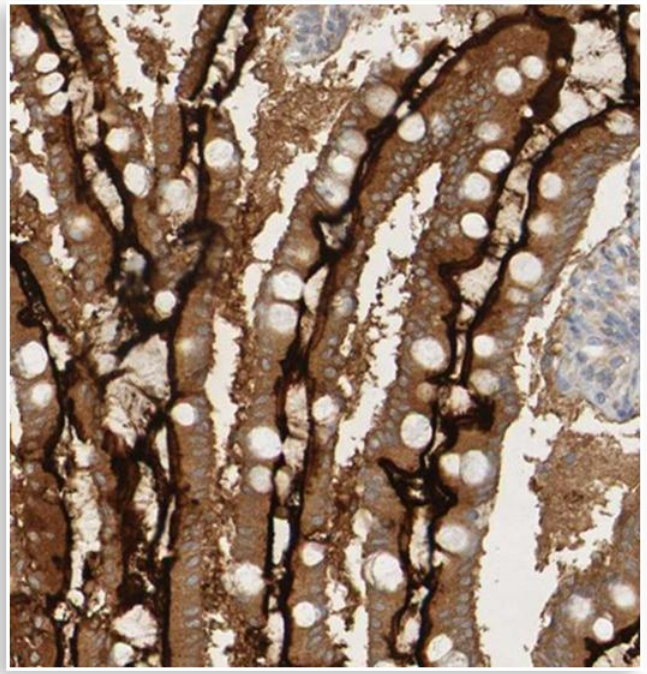


Image reproduced with permission from The Human Protein Atlas (www.proteinatlas.org).

[1]Genetics Home Reference Web site. http://ghr.nlm.nih.gov/gene/LCT. Published October 23, 2012. Accessed February 15, 2013.
[2]Naim HY and Zimmer K-P. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management, 5th ed.* Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.
[3]Perman JA. *Can J Physiol Pharmacol*. 1991;69:111-115.

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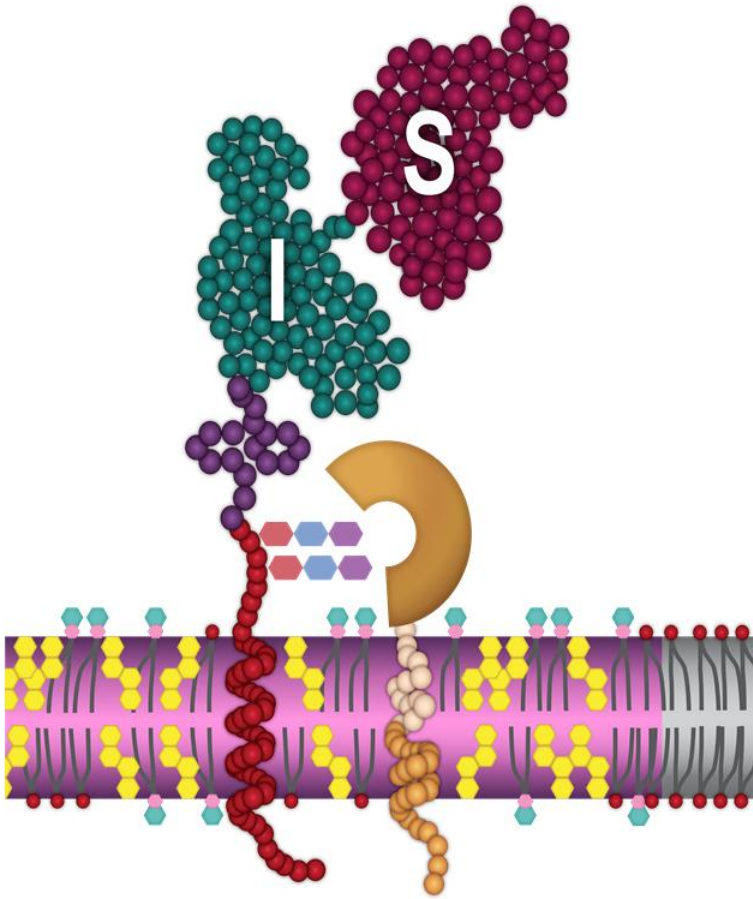
Congenital Sucrase-Isomaltase Deficiency

- CSID is a rare autosomal recessive disorder in which ingestion of sucrose and oligosaccharides leads to malabsorptive diarrhea
- Found in 5% in the native population of Greenland, Alaska, and Canada and 0.02% of people of European descent

Tori AJ, et al. *J Pediatr Gastroenterol Nutr*. 2007;45:194-198.
Gupta SK, et al. *J Pediatr Gastroenterol Nutr*. 1999;28:246-251.
Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.
Alfalah M, et al. *Gastroenterology* 2009;136:883-892.

Congenital Sucrase-Isomaltase Deficiency

- CSID is caused by mutations in the sucrase-isomaltase gene[1-3]
- Several recognized phenotypes result in absence of sucrase, while isomaltase activity varies[1-3]
- Unclear if milder forms exist[4]



Reproduced from the University of Veterinary Medicine Hannover, Foundation Web site.

[1]Alfalah M, et al. *Gastroenterology*. 2009;136:883-892.
[2]Sander P, et al. *Human Mutat*. 2006;27:119.
[3]Jacob R, et al. *J Clin Invest*. 2000;106:281-287.
[4]Karnsakul W, et al. *J Pediatr Gastroenterol Nutr*. 2002;35:551-556.

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Congenital Sucrase-Isomaltase Deficiency

- Reported sucrase-isomaltase mutations disrupt enzyme processing at multiple levels
  - Intracellular processing (glycosylation and folding)
  - Intracellular transport
  - Targeting and insertion of enzyme into brush border membrane

Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14. Naim HY, et al. *J Clin Invest*. 1988;82:667-679. Alfalah M, et al. *Gastroenterology*. 2009;136:883-892. Hauri HP, et al. *Proc Natl Acad Sci USA*. 1985;82:4423-4427. Sander P, et al. *Human Mutat*. 2006;27:119. Jacob R, et al. *J Clin Invest*. 2000;106:281-287.

CSID: Clinical Presentation

- Typical presentation is in infancy, after weaning, with introduction of sucrose-containing foods or drinks (e.g., fruits, juices, and grains)
  - May present earlier if dextrins and isomaltose are present in the diet
- Symptoms include abdominal cramping, bloating, excessive gas, fermentative diarrhea, failure to thrive, and malnutrition

Tori AJ, et al. *J Pediatr Gastroenterol Nutr*. 2007;45:194-198.
Gupta SK, et al. *J Pediatr Gastroenterol Nutr*. 1999;28:246-251.
Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.

CSID: Clinical Presentation

- Most affected children are able to tolerate increased amounts of sucrose and maltose as they grow older
- A number of patients are not diagnosed as children or adults and misdiagnosed as having IBS

Tori AJ, et al. *J Pediatr Gastroenterol Nutr*. 2007;45:194-198.
Gupta SK, et al. *J Pediatr Gastroenterol Nutr*. 1999;28:246-251.
Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.

CSID: Diagnosis

- Stool testing[1,2]
  - pH < 6 suggestive of carbohydrate malabsorption
- Sucrose breath hydrogen testing[2,3]
  - 1-2 g/kg sucrose (≤ 50 g) oral load after 6-hour fast
  - ≥ 10 ppm is positive
  - False positive if rapid intestinal transit
  - False negative if taking antibiotics
- C^{13}-sucrose breath test[4]
  - Preliminary data suggest utility

[1]Naim HY and Zimmer K-P. *Walker's Pediatric Gastrointestinal Disease: Physiology, Diagnosis, Management, 5th ed.* Volume 1. Hamilton, Ontario, Canada: BC Decker Inc; 2008.
[2]Ford RP and Barnes GL. *Arch Dis Child*. 1983;58:595-597.
[3]Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.
[4]Robayo-Torres CC, et al. *J Pediatr Gastroenterol Nutr*. 2009;48:412-418.

CSID: Diagnosis

- Duodenal biopsy and disaccharidase analysis[1]
  - Gold standard
  - Absent sucrase activity and marked reduction of isomaltase activity
  - Normal histology
- Unclear if milder forms exist[2]

[1]Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.
[2]Karnsakul W, et al. *J Pediatr Gastroenterol Nutr*. 2002;35:551-556.

CSID: Dietary Treatment

- Adherence to a sucrose-free diet
- Reduction in starch-containing foods
  - Beetroot, peas, soybean flour, onions
  - Cereals, breads, pastas, and potatoes in the first years of life
  - Avoid glucose polymer formulas and medications with sucrose
- Tolerance improves with age

Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.

CSID: Treatment

- Lyophilized baker's yeast
  - Has sucrase activity but low isomaltase and maltase activity
  - Effective
  - Not very palatable

Treem WR. *J Pediatr Gastroenterol Nutr*. 1995;21:1-14.

CSID: Treatment

- Sacrosidase
  - Has sucrase activity but no isomaltase and maltase activity
  - Approved by US Food and Drug Administration
  - Oral liquid solution used with each meal as replacement
  - Palatable
  - Expensive

Treem WR, et al. *J Pediatr Gastroenterol Nutr*. 1999;28:137-142.

Sarah: Follow-Up

- Breath hydrogen increased by 40 ppm after weight-appropriate sucrose load
- Biopsy results:
  - Complete absence of sucrase activity
  - Reduction in isomaltase and maltase activity

Sarah: Follow-Up

- Sarah diagnosed as sucrase-isomaltase-deficient
- Restrictive diet implemented
  - Avoid sucrose- and starch-containing foods, such as cereals, peas, and sucrose-containing medications

Disaccharidase Deficiencies Related to Specific Diseases

Generalized Malabsorption

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Case Study: Beverly

- 4-year-old Indian American female
- Symptoms
  - Chronic diarrhea for 5 weeks
  - Abdominal bloating and pain

Causes of Disaccharidase Deficiencies

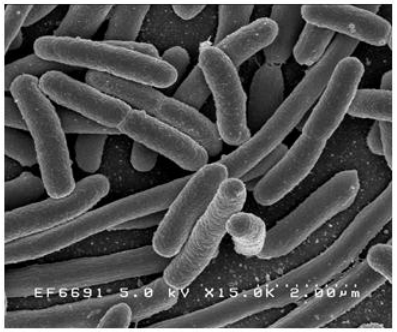
- Brush border defect (primary deficiency: lactase deficiency, sucrase-isomaltase deficiency)
- Disordered motility, leading to small bowel bacterial overgrowth (e.g., primary dysmotility, stricture, short bowel syndrome)
- Mucosal disease (e.g., celiac disease, inflammatory bowel disease, food allergy, infection)

Ushijima K, et al. *Pediatr Clin North Am.* 1995;42:899-915.

Dysmotility

Proximal bowel

1. Dilated bowel/stasis
2. Bacterial overgrowth
3. Secondary inflammation



Distal bowel

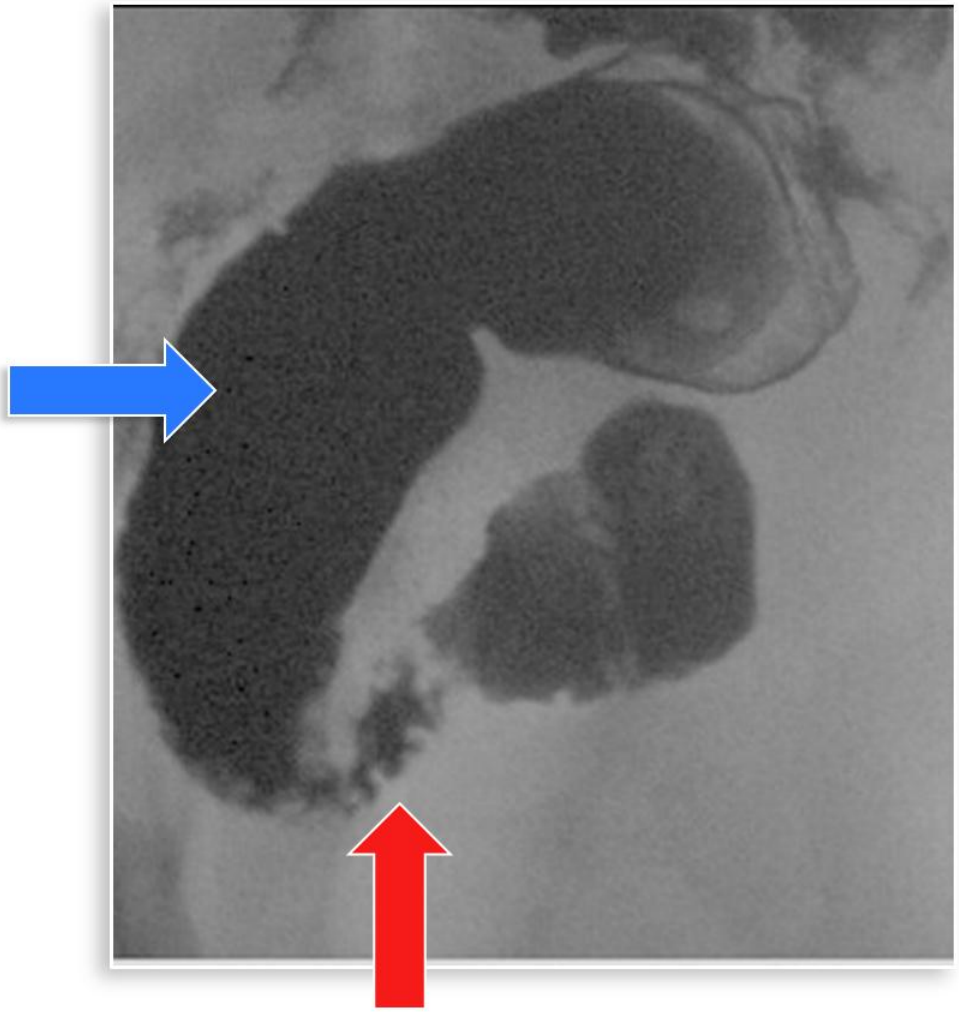
Normal bowel lumen diameter

Stricture

Inflammation leads to disaccharidase loss on enterocyte surface

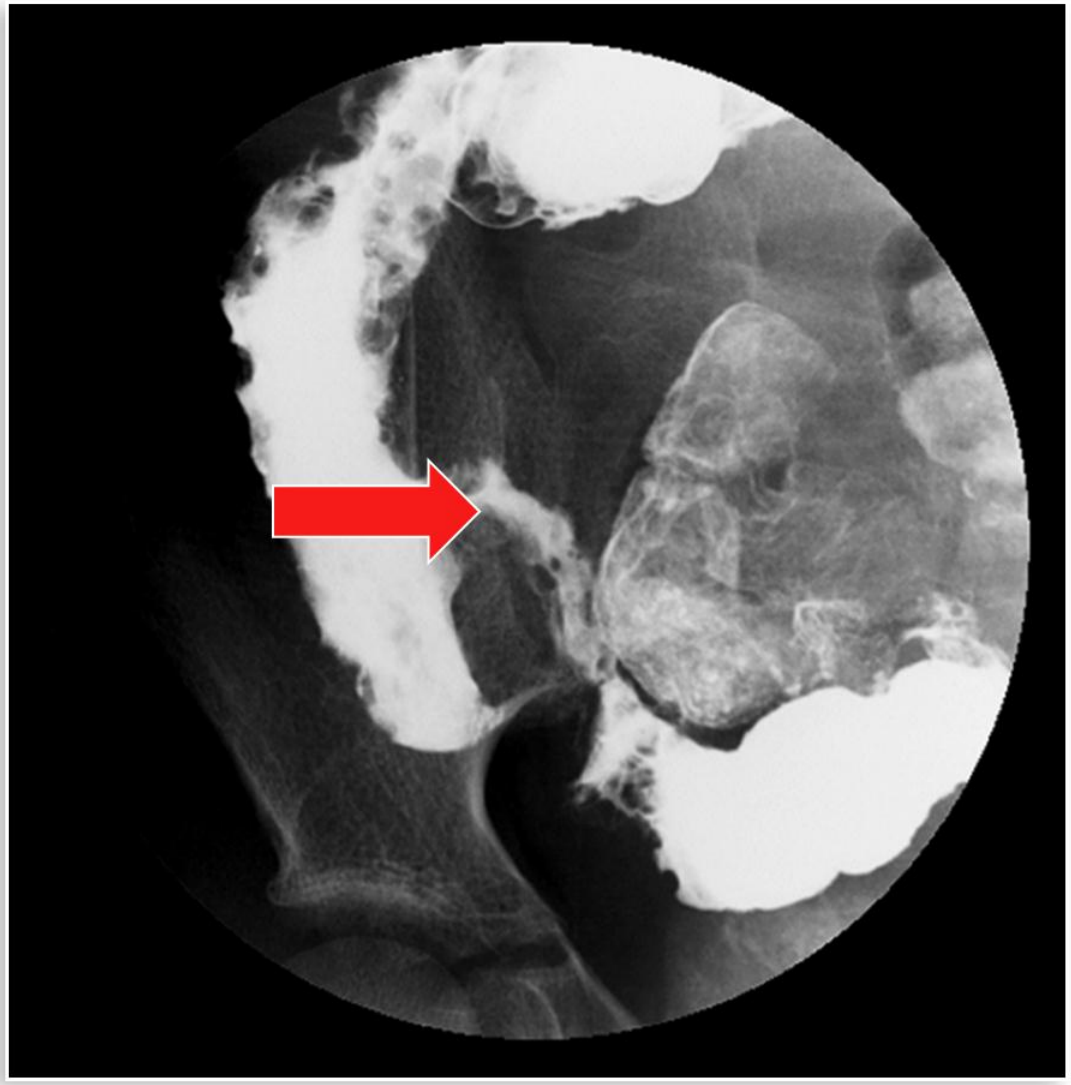
Kastin DA and Buchman AL. *Curr Opin Gastroenterol.* 2002;18:221-228.

Dysmotility



Intestinal stricture (red arrow) with dilated proximal small bowel (blue arrow) in patient with short bowel syndrome

Dysmotility

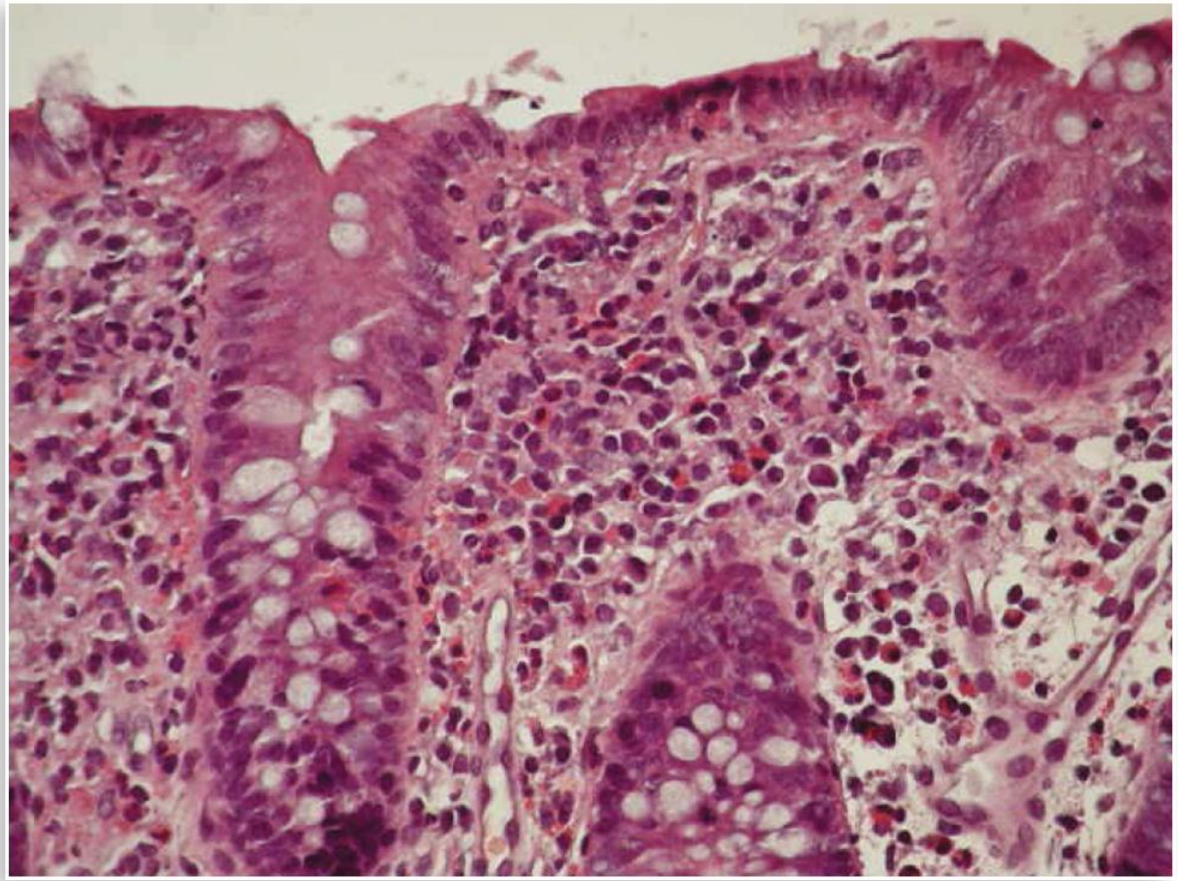


Ileal stricture from Crohn's disease

Mucosal Disease

- Any inflammation of the small intestine epithelium can potentially lead to a secondary loss of disaccharidases
  - Food allergy
  - Inflammatory bowel disease (Crohn's disease)
  - Celiac disease
  - Giardiasis

Mucosal Disease: Allergic

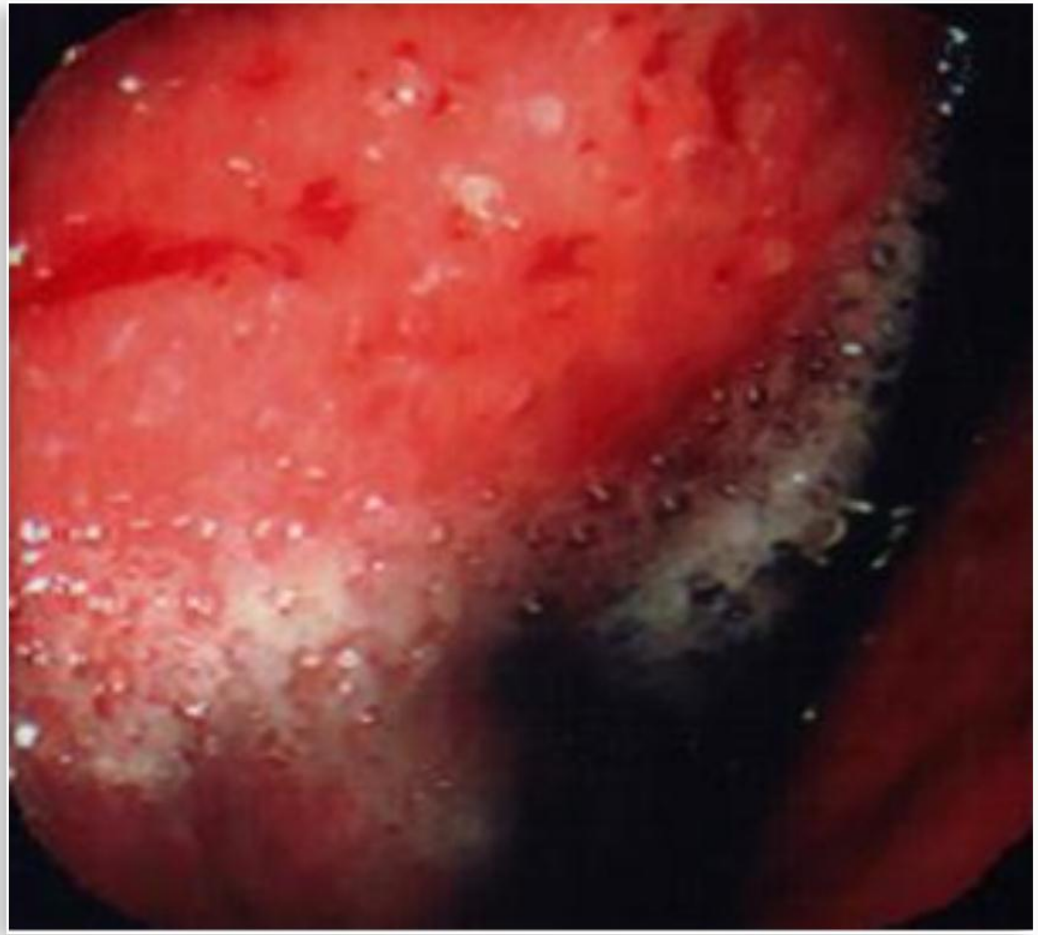


Eosinophilic infiltration of intestine due to cow's milk protein allergy in an infant

Reproduced from Lucarelli S, et al. *BMC Gastroenterol.* 2011;11:82.

Lucarelli S, et al. *BMC Gastroenterol.* 2011;11:82.

Mucosal Disease: Crohn's Disease

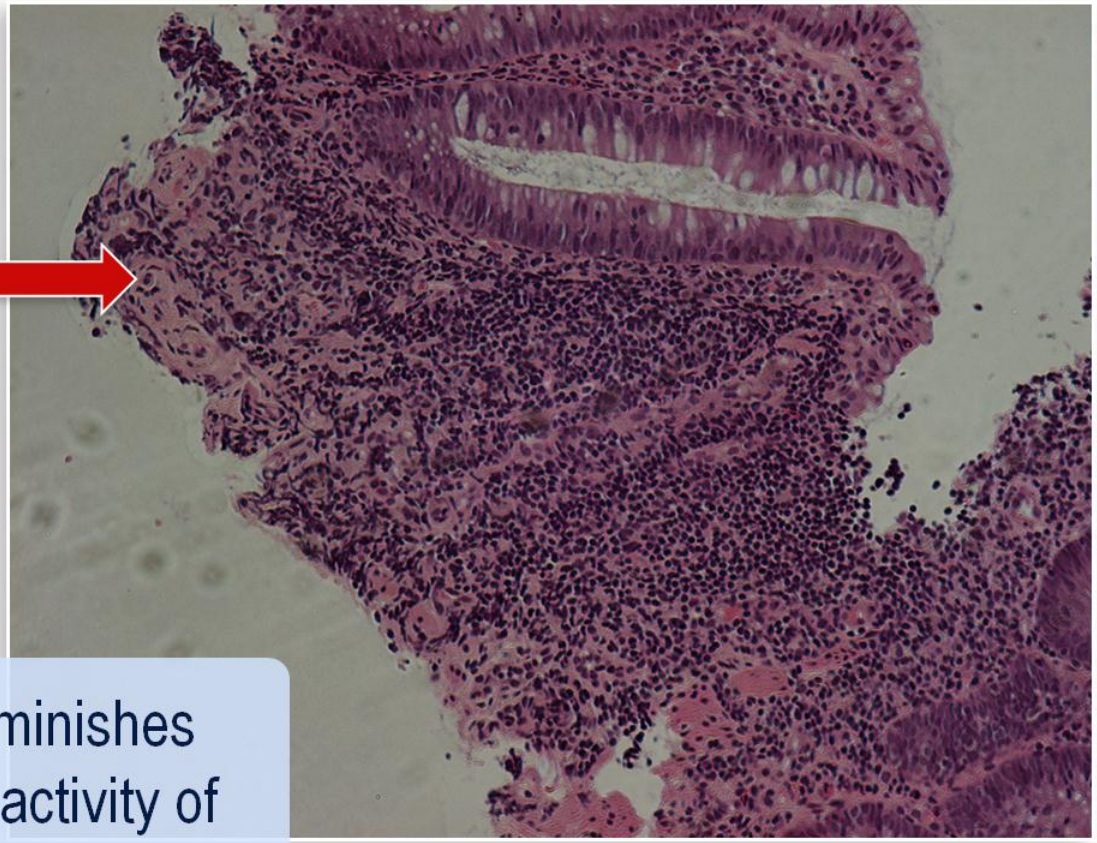


Crohn's disease with small intestinal inflammation

May present in a manner similar to IBS

Mucosal Disease: Crohn's Disease

Characteristic granuloma



- Inflammation diminishes disaccharidase activity of small bowel

Pfefferkorn MD, et al. *J Pediatr Gastroenterol Nutr.* 2002;35:339-343.

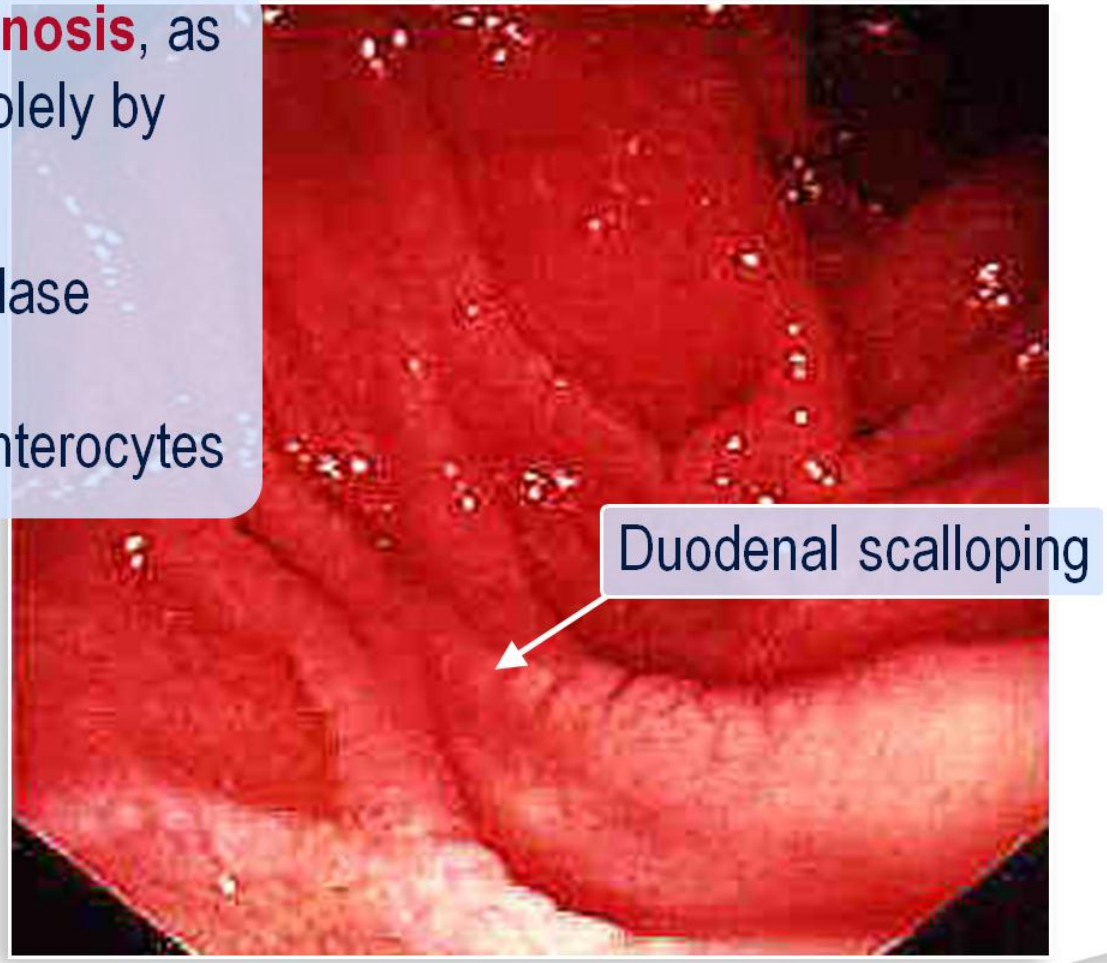
Mucosal Disease: Celiac Disease - History

- Symptoms described by Samuel Gee in 1888[1]
- Dicke and van de Kamer: identified alcohol soluble fraction of wheat gluten (**gliadin**) and similar residues in related barley, rye, and oats as being the damaging agents[2]

[1]Gee SJ. *St Bartholomew's Hospital Report.* 1888;24:17-20.
[2]Dicke WK, et al. *Acta Paediatr.* 1953;42:34-42.

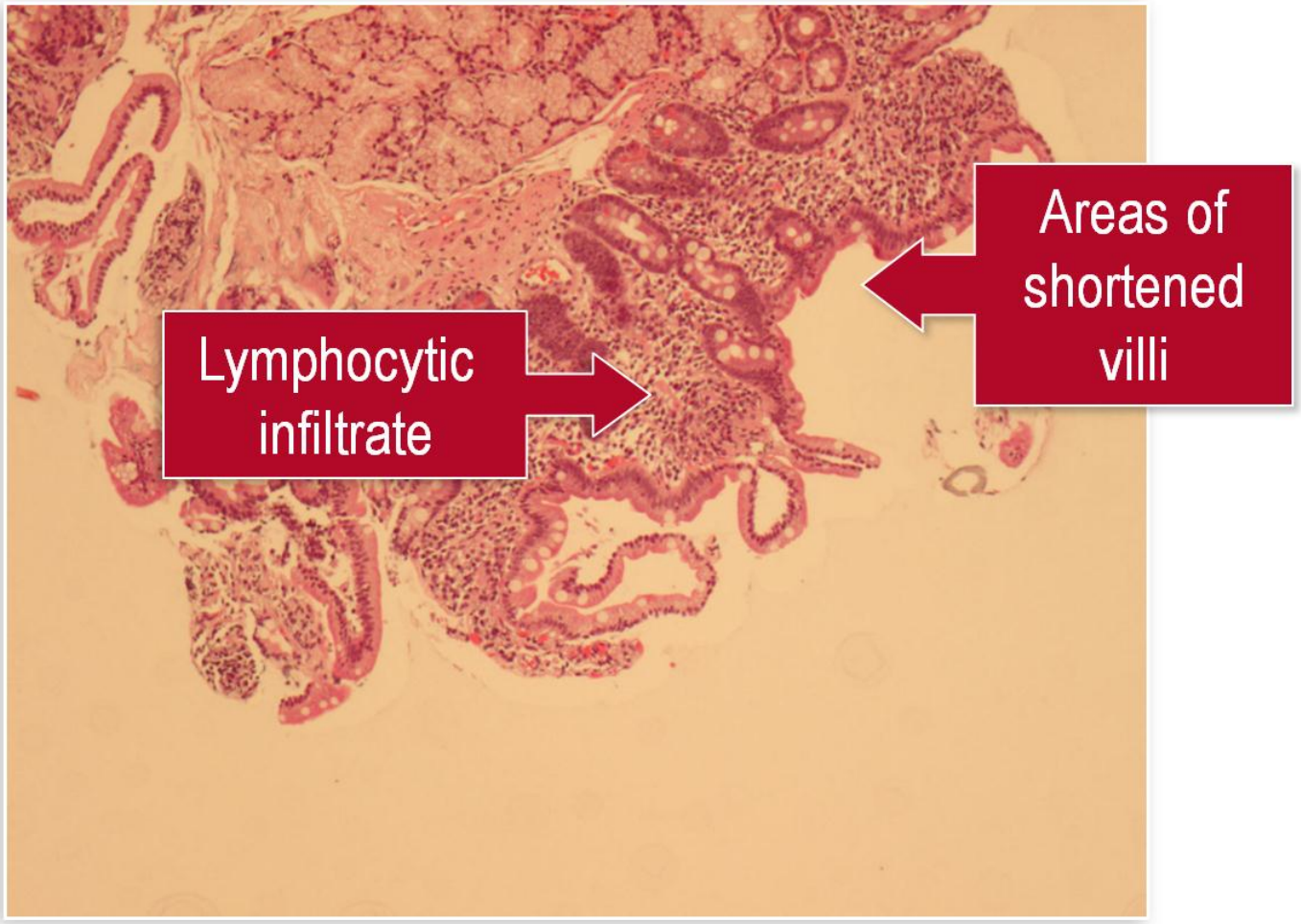
Mucosal Disease: Celiac Disease

- **Biopsy is key to diagnosis**, as diagnosis cannot be solely by visual examination
- Secondary disaccharidase deficiency due to inflammation/loss of enterocytes



Oxentenko AS, et al. *Am J Gastroenterol.* 2002;97:933-938.

Mucosal Disease: Celiac Disease

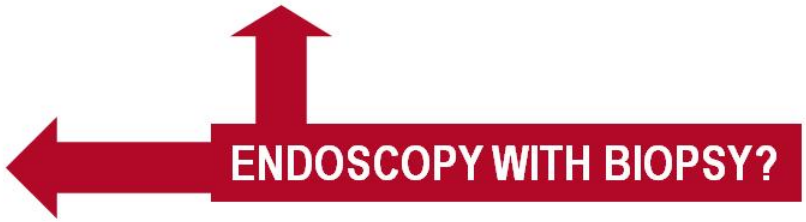


Lee SK and Green PH. *Curr Opin Gastroenterol.* 2005;21:589-594.

Evaluation of Dysmotility and Mucosal Disease: Potential Pertinent Tests

- Blood tests
  - Complete blood count, erythrocyte sedimentation rate, C-reactive protein
  - Tissue transglutaminase and immunoglobulin A (IgA)
  - T4/thyroid-stimulating hormone
- Stool tests
  - Culture, *C. difficile* toxin
  - Calprotectin
  - Reducing substances, pH
- Urine culture
- Breath hydrogen testing

- Radiographic tests
  - Abdominal x-ray
  - Abdominal ultrasound
  - Magnetic resonance enterography
  - Abdominal computed tomography
  - Upper gastrointestinal (GI) ± small bowel follow-through



Zella GC and Israel EJ. *Pediatr Rev.* 2012:33:207-218.

Celiac Disease: Treatment

- Removal of gluten is essential
- Lifelong adherence to a gluten-free diet currently recommended

Celiac Disease Foundation Web site. http://www.celiac.org/images/stories/PDF/quick-start.pdf. Accessed February 15, 2013.

Celiac Disease: Treatment

- **Foods to avoid**
  - Grains and flours
    - All flours containing wheat, rye, barley, and oats
  - Breads
    - All breads containing wheat, rye, barley, and oats
  - Cereals
    - All cereals containing wheat, rye, barley, and oats
  - Noodles and pasta
    - Any type made of wheat, rye, barley, and oats
  - Alcohol derived from grain (adolescent/adult issue)

Celiac Disease Foundation Web site. http://www.celiac.org/images/stories/PDF/quick-start.pdf. Accessed February 15, 2013.

Celiac Disease: Treatment

- **Foods to allow**
  - Grains and flours
    - Almond, arrowroot starch, artichoke, corn starch, cornmeal, maize, legumes, potato starch, rice bran, rice flours, sesame, soybean flours, sunflower, tapioca starch
  - Breads
    - Only those breads with allowed gluten-free flours (see above)
  - Cereal
    - Cereal from corn, rice, or hominy
  - Noodles and pasta
    - Gluten-free corn, rice, or bean pasta

Celiac Disease Foundation Web site. http://www.celiac.org/images/stories/PDF/quick-start.pdf. Accessed February 15, 2013.

Beverly: Follow-Up

- Serum tissue transglutaminase IgA antibody positive
- Duodenal scalloping visible on upper GI endoscopy
- Characteristic findings on duodenal biopsy
- Beverly is diagnosed with celiac disease
- Started on gluten-free diet
  - No foods containing wheat, rye, or barley

Fasano A and Catassi *C. N Engl J Med.* 2012;367:2419-2426.

Functional Diarrhea in Toddlers

Toddler's Diarrhea/Chronic Nonspecific Diarrhea of Infancy

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

Case Study: Owen

- 2-year-old Caucasian male
- Symptoms
  - Intermittent diarrhea over last 3 months
    - No effect on weight gain or activity level
    - Stools shortly after eating
    - Mushy to watery
  - Drinks 5-6 cups of juice daily
  - Family friend recommended low fat diet, which made diarrhea worse

Functional Diarrhea in Toddlers: Overview

- Term first coined in 1956 by Cohlan[1]
- Described by Davidson and Waserman in a 1966 series of 186 children[2]
- Little research on the disorder in the last 20 years

[1]Cohlan SQ. *Pediatrics*. 1956;18:424-432.
[2]Davidson M and Waserman R. *J Pediatr*. 1966;69:1027-1038.

Functional Diarrhea in Toddlers: Etiology

- Etiology not evident in all cases
- Dietary nutritional imbalance often responsible
  - Increased intake of poorly absorbed sugars, often from fruit juice
  - Reduced intake of fat and fiber

Hyman PE, et al. *Gastroenterology*. 2006;130:1519-1526.

Functional Diarrhea in Toddlers: Presentation

- 12% begin between birth and 5 months of age
- > 75% begin between 6 and 20 months of age
- 88% resolve by 39 months of age
  - 98% by 48 months of age
- First stool of the day often more formed than subsequent ones

Davidson M and Waserman R. *J Pediatr*. 1966;69:1027-1038.

Functional Diarrhea in Toddlers: Presentation

- Daily painless passage of ≥ 3 large, unformed stools
  - May contain food and mucus
  - Often foul-smelling
- Symptoms last > 4 weeks
- Passage of stool during waking hours
- No failure to thrive if caloric intake adequate

Hyman PE, et al. *Gastroenterology*. 2006;130:1519-1526.

Functional Diarrhea in Toddlers: Diagnosis

- Clinical diagnosis
- Requires very detailed history
- Exclude possibility of
  - Enteric infections (including Giardia)
  - Antibiotics
  - Laxatives
  - Celiac disease
  - Disaccharidase deficiency

Hyman PE, et al. *Gastroenterology*. 2006;130:1519-1526.

Functional Diarrhea in Toddlers: Diagnosis

- Dietary history critical
- Overfeeding
  - Excessive fluid intake (> 190 $mL \cdot kg^{-1} \cdot d^{-1}$)
- Excessive fruit juice intake
  - Fructose, sorbitol
- Low fat intake
  - ≤ 27% of calories
- Food allergy

Kneepkens CM, et al. *Eur J Pediatr*. 1989;148:571-573.
Hoekstra JH, et al. *Arch Dis Child*. 1995;73:126-130.
Cohen SA, et al. *Am J Dis Child*. 1979;133:490-492.

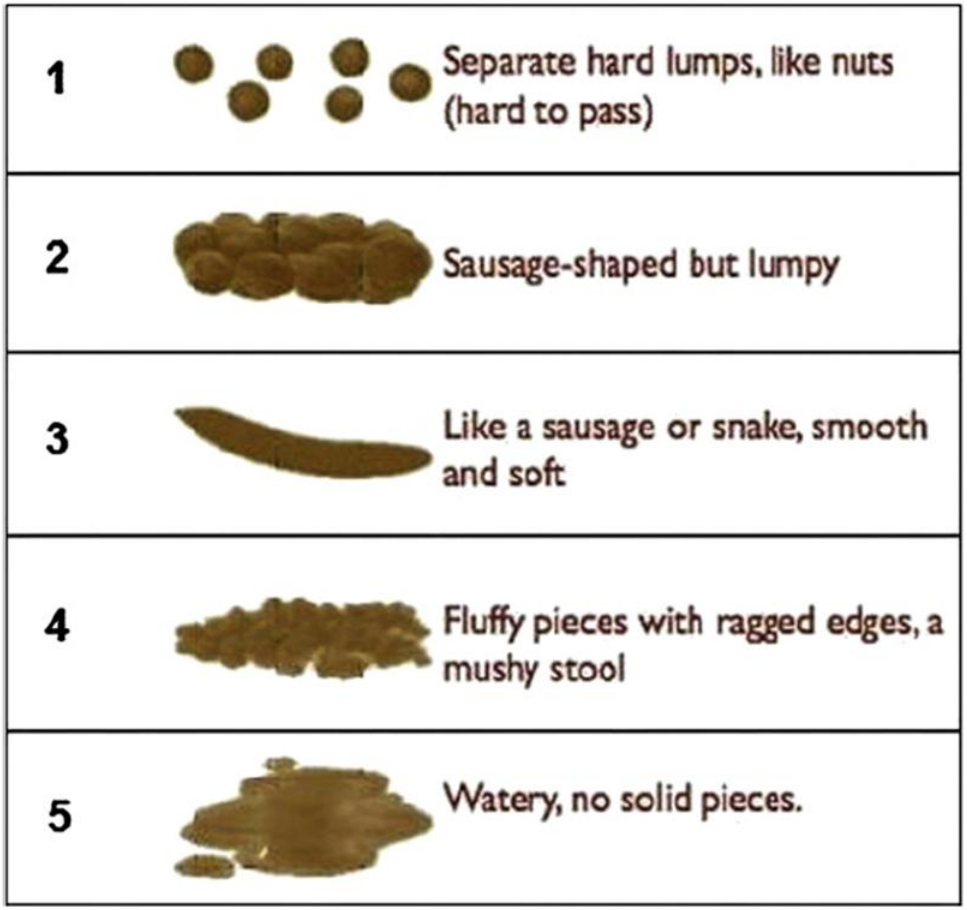
Functional Diarrhea in Toddlers: Treatment

- 80% improved on a normal diet for age
  - Appropriate fat, carbohydrate, and protein ratio
  - Limiting juice and excessive fluid intake
- Psyllium can be used as a bulking agent (1 tbsp twice daily)

Davidson M and Waserman R. *J Pediatr*. 1966;69:1027-1038.
Smalley JR, et al. *J Pediatr Gastroenterol Nutr*. 1982;1:361-363.
Boyne LJ, et al. *Pediatrics*. 1985;76:557-561.

Functional Diarrhea in Toddlers: Treatment

- Ask parents to keep diet and stool diary for 1 week
  - Diarrhea has been reported to resolve during the observation period
  - Use of pediatric stool chart objectifies report



Boyne LJ, et al. *Pediatrics*. 1985;76:557-561.
Lane MM, et al. *J Pediatr,* 2011;159:437-441.

Functional Diarrhea in Toddlers: Patient Education

- Balanced diet for age cornerstone of treatment
- Consultation with a dietitian may be helpful
- Reassurance that there are no known long-term consequences of the disorder
- Discussion of the utility of keeping a diet and stool diary

Owen: Follow-Up

- Growth parameters normal
- Examination of stool showed no pathogens or blood
- Owen diagnosed with functional diarrhea
- Juice intake restricted and fat and fiber dietary content increased (appropriate diet for age); stool consistency improved and normal growth continued
- Parents advised to keep daily diet/defecation diary for 1 week

Summary

- Carbohydrates are a critical dietary component, especially in growing children
- Carbohydrate malabsorption creates a barrier to development
  - Consideration of the diagnosis can quickly establish cause of symptoms
  - Appropriate treatment reduces symptoms and ensures patients receive essential nutrients
- Education on appropriate adjustment to carbohydrate intake empowers parents to regain control of their child's nutrition